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ANNALS OF SAUDI MEDICINE

Aims and Scope

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The *Annals* is a bimonthly multidisciplinary medical journal. High-quality papers written in English, dealing with aspects of clinical, academic or investigative medicine or research will be welcome. Emphasis is placed on matters relating to medicine in Saudi Arabia in particular, and the Middle East in general, though articles are welcome from anywhere in the world, and the *Annals* has worldwide readership.

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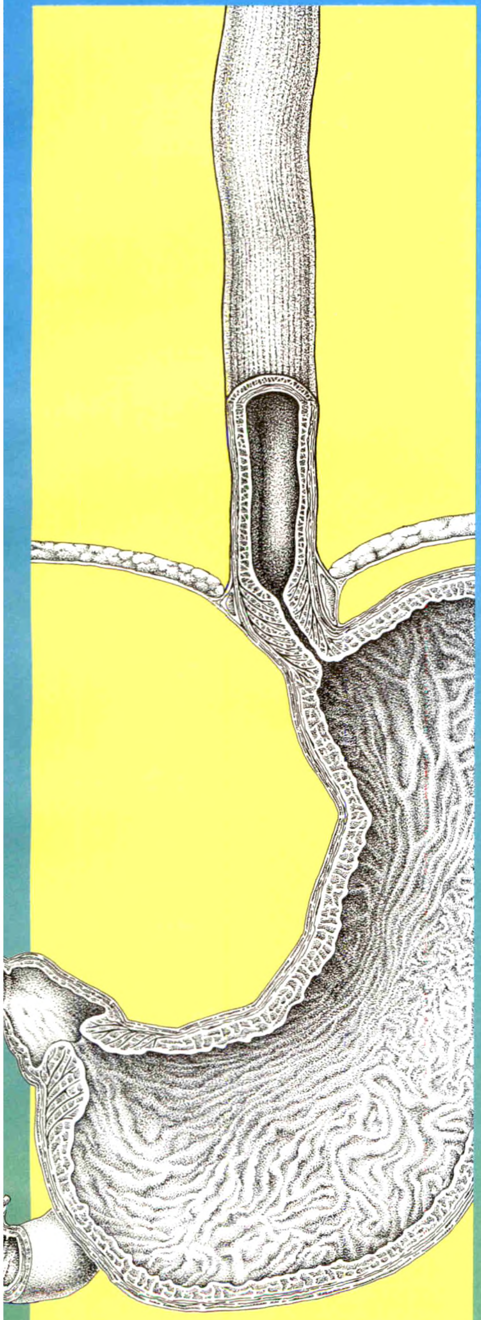

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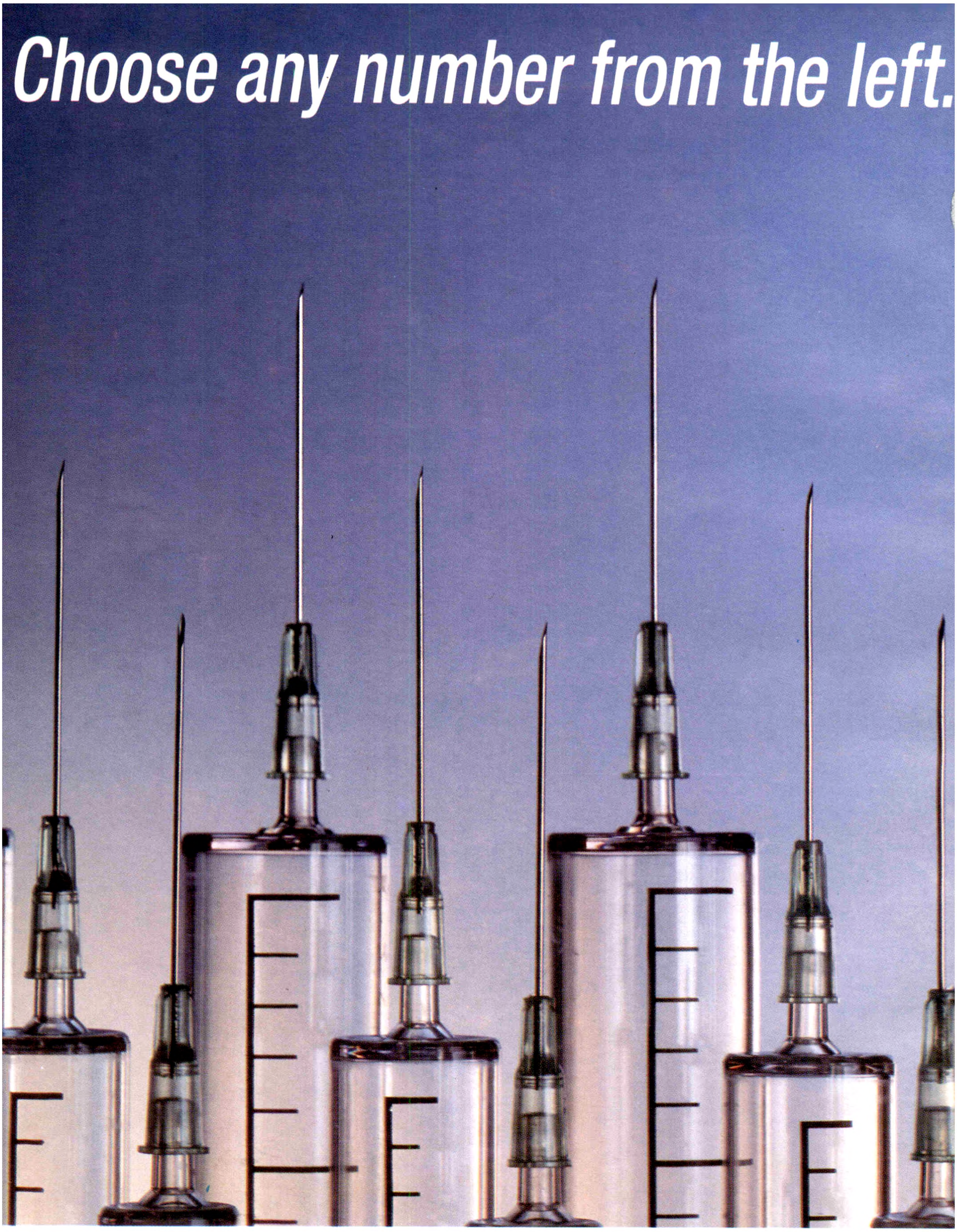

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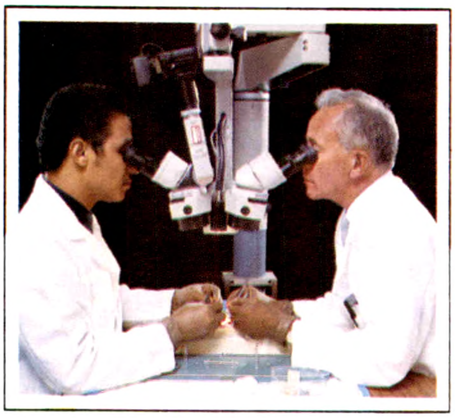

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Editorial

SAUDI BOARD FOR HEALTH SCIENCES: THE EXPECTATIONS AND THE CHALLENGES

On 30 Rabi-Al-Thani 1407H (31 December 1986G) a meeting on organizing postgraduate medical education studies in Saudi Arabia was held at the Ministry of Higher Education. The meeting was addressed by the Minister of Higher Education, H.E. the late Sheikh Hassan Aal-Alshiek. The Ministry of Higher Education invited all the deans of colleges in medicine, dentistry, pharmacy, and applied health sciences as well as the directors of postgraduate medical education and representatives from Ministry of Health, Ministry of Defense, Ministry of Interior, National Guard, King Faisal Specialist Hospital and Research Centre (KFSH&RC), Arabian American Oil Company (ARAMCO), Civil Bureau, and Joint Board for Postgraduate Medical Education to attend this meeting [1,2].

The meeting ended with the recommendation to develop a Saudi Board for Health Sciences (SBHS). The primary function of SBHS will be to supervise all postgraduate training programs in medicine, dentistry, pharmacy, and applied medical sciences by establishing a scientific council for every specialty. Each scientific council will then be fully responsible for all aspects of training, accreditation of training centers, and certification in the relevant specialty.

The Council of Ministers, at its meeting on 6 Safar 1413H (4 August 1992G), chaired by The Custodian of the Two Holy Mosques, King Fahd Bin Abdul Aziz, approved the establishment of the SBHS. The Council declared the SBHS a scientific professional board with its main office in Riyadh, which may have chapters in other cities in the Kingdom. This approval was well received by all health care professionals throughout the Kingdom. The support and efforts of the Minister of Higher Education, H.E. Dr. Khalid Al-Anqari, and the Minister of Health, H.E. Mr. Faisal Al-Hujailan, are recognized and appreciated by all concerned in the organization of postgraduate medical education in Saudi Arabia.

The Council also approved H.E. the Minister of Health as the Chairman of the Board of Trustees for the SBHS. Other trustee members will include three from the Ministry of Health; four deans from the health sciences colleges (medicine, dentistry, pharmacy, applied medical sciences); one from each of the medical services in the Ministry of Defense, Ministry of Interior, and the National Guard; and three from the non-governmental sector. The General Secretary will be chosen by the trustees.

Establishing the bylaws will be the responsibility of the Board of Trustees. However, to enable the SBHS to accomplish its goals of supervising postgraduate medical education in Saudi Arabia, coordinating continuing medical education programs, and establishing standards in every speciality, the SBHS is expected to take a role similar to other professional boards such as the American Board, Canadian Board, and the Royal Colleges in the United Kingdom regarding certification, accreditation of training, and establishment of standards for the specialty and standards for medical ethics. The SBHS will be involved in registering and granting permission to practice in Saudi Arabia; it will set up the guidelines similar to other professional bodies such as the British Medical Council. It is also expected that the SBHS will promote and fund scientific research in all specialties of the health sciences. These are some of the expectations from the SBHS.

On the other hand, the SBHS will be facing some problems and challenges. The first problem relates to financial resources. Although the SBHS will be inheriting about 10 million Saudi riyals from the Joint Board for Postgraduate Medical Education, a major portion of its income will come from the annual fees of its members. It is expected that all practicing health professionals in Saudi Arabia will be active members and will pay membership fees. Another source of income will consist of the money paid by governmental agencies that have members on the Board of Trustees who benefit from the services of the SBHS. These agencies include the Ministry of Health, Ministry of Higher Education, Ministry of

Defense, Ministry of Interior, and the National Guard Medical Service. However, as time passes, more income will come from the examination and registration fees from the courses and symposia which the SBHS will organize and coordinate.

The second problem is organizing and coordinating existing and future training programs. The SBHS will face some difficulties in unifying the training programs of each specialty. The same could be said about coordinating the continuing medical education programs in Saudi Arabia. Presently, many agencies are organizing these activities without coordinating with one another, and this leads to duplication of activities. The organization and coordination of training and continuing medical education programs will be the two important functions of the SBHS.

All governmental and non-governmental agencies should help the SBHS achieve its goals. I am optimistic that they will do so. It has been almost six years since the idea of establishing the SBHS was initiated by the Ministry of Higher Education. It was like a dream, and now is becoming a reality [2]. I am confident that before another six years pass, the SBHS will be achieving most of its goals and will be a leader in postgraduate and continuing medical education in Saudi Arabia and abroad.

Mansour Al-Nozha, FRCP(Lond), FRCP(E), FRCP(I)
Professor of Medicine
Dean, College of Medicine
King Saud University
P.O. Box 2925
Riyadh 11461, Saudi Arabia

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Original Articles

PREVALENCE OF HEPATITIS B SURFACE ANTIGENEMIA AMONG PATIENTS WITH SCHISTOSOMA MANSONI

Hussein M. Al-Freihi, MD

صممت هذه الدراسة المقارنة لتحديد انتشار المستضد السطحي لالتهاب الكبد المعند بالحُمة ب في دماء المـرضى المصابين بالمنشقة المنسونية ولتبرير الحاجة إلى تلقيحهم ضد التهاب الكبد بالحُمة ب. تمت مطابقة ٧٠ مريضا على التوالي ممن تأكد تشخيص المنشقة المنسونية لديهم من حيث عوامل العمر والجنس والجنسية ومكان الإقامة (للسعوديين فقط) مع مجموعة ضابطة مؤلفة من ٧٠ شخصًا من الأصحاء. وعلى الرغم من تطابق متوسط الأعمار والجنس وتوزيع الجنسيات، إلا أن ١٨ مريضًا بداء المنشقات (٢٦٪) كانوا يحملون إيجابية للمستضد السطحي لالتهاب الكبد ب مقارنة بثلاثة فقط (٤٪) من المجموعة الضابطة. كانت نسبة الأرجحية = ٧,٧٣ للمستضد السطحي لإلتهاب الكبد ب بين المرضى لدى مقارنتهم بالمجموعة الضابطة (حدود ٩٥٪ للوثوق = ٢ ـ ٣٥,٠١ ودرجة الاحتمال P = ٠,٠٠٠٤). لم يكن للجنس أو الجنسية أي تأثير في معدل إيجابية المستضد السطحي لالتهاب الكبد ب لدي مرضى داء المنشقات. وجدنا لدى مرضى داء المنشقات حاملي إيجابية المستضد السطحي لالتهاب الكبد ب خللاً أكبر في إنظيمات الكبد) ١٤ من كل ١٨، ٧٨٪ (مقارنة بمن لا يحملون هذا الواسم المصلي للحمة) ٢٢ من كل ٥٢، ٤٢٪) (نسبة الأرجحية ٤,٧٧ درجة الاحتمال P = ٠,٠٠٩ حدود ٩٥٪ للوثوق = ١,٢٢ ـ ٢٠). أخلص إلى القول بأن مرضى المنشقة المنسونية هم أكثر تعرضًا للإصابة بالتهاب الكبد بالحُمة ب وأن لمشاركة داء المنشقات مع التهاب الكبد بالحُمة ب تأثيرًا سيئًا على إنظيمات الكبد ووظائف الكبد الأخرى. لذا فإنه من الضروري إجراء تقييم استطلاعي للدور الوقائي للقاح التهاب الكبد بالحُمة ب لدى هؤلاء المرضى.

This case-control study was designed to determine the prevalence of persistent hepatitis B surface antigenemia (HBsAG) among patients with schistosoma mansoni and to rationalize their vaccination against hepatitis B virus (HBV) infection. Seventy consecutive patients with a confirmed diagnosis of schistosoma mansoni were matched for age, sex, nationality, and residence (for Saudis only) with 70 healthy controls. Despite identical mean ages, sex, and nationality distribution, 18 schistosomiasis patients (26%) had positive HBsAg as compared with only three of the controls (4%). The odd ratio for HBsAg antigenemia among patients as compared to controls was 7.73 (95% confidence interval (CI) = 2-35.01, $P = 0.0004$. Neither sex nor nationality had any influence on the positive rate for HBsAg found in schistosomiasis patients. Patients with schistosomiasis and a concomitant positive HBsAg had significantly more derangement of their hepatic enzymes (14 out of 18; 78%) as compared with those without this viral serological marker (22 out of 52; 42%) (odd ratio - 4.77; 95% CI=1.22-20.11; $P = 0.009$). I have concluded that patients with schistosoma mansoni are exposed to a higher risk of acquiring HBV infection and that concomitant schistosomiasis and HBV infection has a deleterious effect on hepatic enzymes as well as other liver functions. Prospective evaluation of the preventive role of HBV vaccine among these patients is warranted.

Since the discovery of hepatitis B virus surface antigen (HBsAg) in 1964 by Blumberg et al [1], there has been an increased body of evidence about hepatitis B viral (HBV) infection worldwide. Extensive data pertinent to this disease are now available; its prevalence, incidence, mode of transmission, clinical features, complications,

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From the Department of Medicine, King Fahd Hospital of the University, Al-Khobar.

Address reprint requests and correspondence to Dr. Al-Freihi: Associate Professor of Medicine, King Fahd Hospital of the University, Al-Khobar, P.O. Box 40004, Al-Khobar 31952, Saudi Arabia.

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serological markers, and as of lately, prevention [2].

The prevalence of the disease is known to show a significant geographical variation [2]. While a low HBsAg positive rate of only 0.2% was reported among American blood donors [3], a positive rate of 8.5% was detected in 2,487 male Saudi blood donors [4]. A review of all survey studies regarding HBV serological markers in various regions throughout the country showed cumulative positivity rates of 10.2% and 6.4% among Saudi males and females, respectively [5]. In Khaibar (near Medina), an extremely high rate of up to 80% has been reported [6]. In another study of 500 consecutive admissions to King Faisal Specialist Hospital and Reseach Centre (KFSH&RC) located in Riyadh, Saudi Arabia, evidence of at least one positive HBV marker was found in 56.6% of patients [7].

Considering the high endemicity rate of HBV infection in the Kingdom and its serious consequences, a comprehensive program for vaccination of identified risk groups against HBV infection should be initiated. Therefore, it is prudent that we should attempt to identify yet unknown high-risk groups. One potential group of such patients includes those with schistosoma mansoni infection which is another prevalent disease in the Kingdom. As early as 1967, endemicity of schistosomiasis has been reported from various regions throughout the Kingdom, particularly in the Southwest [8].

As schistosoma infestation appears to be more endemic in the same areas as HBV infection and that dual infection with schistosoma mansoni and HBV may lead to severe liver disease; victims of schistosomiasis and those exposed to it may be considered as a potential group to benefit from an HBV vaccine. As the exact prevalence of HBV infection in these patients is not yet known in Saudi Arabia, this retrospective case-control study was designed to demonstrate the prevalence of HBsAg antigenemia among patients with schistosoma mansoni as compared to their matched control.

Material and Methods

This is a retrospective case-controlled study which was conducted at King Fahd Hospital of King Faisal University, Dammam, Saudi Arabia. The sample size was determined based on the following assumptions: the prevalence rate of HBV exposure in the Southern region of the Kingdom or in other Arab countries is around 15% [5] with a projected prevalence of HBV among bilharzial patients of 25-30%. For a study with a power of 80% and Type-1 error of 5%, an estimated number of 70 patients with hepatosplenic schistosomiasis and another 70 paired controls were needed.

Patients were identified from the outpatient logbooks and from the hospital's computerized database. The first consecutive 70 patients with a confirmed diagnosis of chronic schistosoma mansoni infestation in whom the HBsAg status was known, were considered eligible. Confirmed diagnosis of eligible patients was based on the presence of hepatomegaly and/or splenomegaly including one or more of the following criteria: positive stool for bilharzial ova, demonstration of bilharzial ova by rectal snip, or identification of bilharzial granuloma on liver biopsy. Eligible non-Saudi patients were also included. To determine the relative risk for acquiring HBV infection in schistosoma patients, the prevalence rate of HBsAg was determined in a consecutive 70 controls. All patients with positive HBsAg test had a repeated test after an average period of four to eight months. For each patient, one control with a known HBsAg status was identified prospectively and matched for age, sex, occupation, and nationality. Fifty-three of the controls were healthy blood donors and the remaining 17 controls were recruited from the outpatient clinics provided they had no known risk of acquiring liver disease or hepatitis. For Saudi patients, matching for region of residence was mandatory. Schistosoma patients or controls who were exposed to any of the known risk factors were excluded. All patients with schistosomiasis had their liver enzymes measured. On the other hand, albumin and/or prothrombin time were estimated in several patients. All liver enzymes and other function parameters were estimated using the calorimetric method while the enzyme-linked immunosorbent assay (ELISA) was used to determine the HBsAg status.

Comparisons of categorized characteristics of patients and their matched controls were carried out using the chi-square test with correction for continuity or Fisher's exact tests where appropriate. The two-tailed t-test was used to compare the means of continuous variables. The odd ratios of positive serology for HBsAg and for the prevalence of abnormal liver enzymes were measured using Mantel-Hanzesel statistics. All statistical analyses were carried out using BMDP statistical software [9].

Results

In reviewing the medical records of approximately 250 patients with chronic schistosoma mansoni infestation, 70 consecutive patients were identified with known HBsAg status. The latter 70 eligible patients were matched for age, sex, nationality, and place of residence (for Saudis only) with 70 controls (Table 1). The mean age (±SD) was 37.4 (±12.6) and 37.4 (±12.1) years for patients and controls, respectively. Male to female ratio was comparable among patients and controls. In each group, 57 (81%) were males and 13 (19%) females. Distribution of nationalities was also identical in the two groups. In each group, 16 (23%), 39 (55.5%), 13 (18.5%), and 2 (3%) individuals were Saudi, Yemeni, Egyptian and other nationalities, respectively.

TABLE 1. *Demographic and clinical characteristics of patients and controls.*

Characteristics	Patients No. (%)	Controls No. (%)
Nationality		
Saudi	16 (23)	16 (23)
Yemeni	39 (56)	39 (56)
Egyptian	13 (18)	13 (18)
Other	2 (3)	2 (3)
Southern Saudis only	16 (23)	16 (23)
Abnormal LFTs (abnormal/no.)		
HBsAg positive	14/18 (78)	2/3 (66)
HBsAg negative	22/52 (42)	6/67 (9)
Low albumin (abnormal/no. tested)		
HBsAg positive	11/18 (61)	non-tested
HBsAg negative	9/21 (43)	non-tested

LFTs = liver function tests.

TABLE 2. *Prevalence of HBsAg antigenemia among patients and controls according to nationality.*

Group	Nationality	Negative HBsAg (%)	Positive HBsAg (%)	Total (%)
Controls	Saudi	14 (94)	2 (6)	16 (100)
	Yemeni	38 (97)	1 (3)	39 (100)
	Egyptian	13 (100)	0 (0)	13 (100)
	Other	2 (100)	0	2 (100)
Subtotal		67 (96)	3 (4)	70 (100)
Patients	Saudi	12 (75)	4 (25)	16 (100)
	Yemeni	28 (72)	11 (28)	39 (100)
	Egyptian	10 (77)	3 (23)	13 (100)
	Other	2 (100)	0	2 (100)
Subtotal		52 (74)	18 (26)	70 (100)
Total		119 (85)	21 (15)	140 (100)

Table 2 shows that of the 70 schistosomiasis patients, 18 (26%) were seropositive for HBsAg as compared with 3 of 70 controls (4%). The odds ratio for HBsAg antigenemia among patients as compared to controls was 7.73 (95% confidence interval, (CI)=2-35.01). Mantel-Hanzesel statistics were found to be highly significant ($P = 0.0004$).

Table 2 also shows the distribution of HBsAg antigenemia among patients and controls classified according to nationality. No statistically significant difference was noted in the positive rates of HBsAg between Saudis, Yemeni, and Egyptian patients.

Analysis of the distribution of HBsAg antigenemia among schistosomiasis patients according to gender was also performed. This demonstrated that 14 of 57 males (25%) and 4 of 13 females (31%) were seropositive. The latter difference was not found to be statistically significant ($P = 0.9$).

Analysis of levels of liver enzymes among schistosomiasis patients and controls was also performed (Table 1). The latter table demonstrated that of 52 patients who tested negative for HBsAg, only 22 (42%) had one or more abnormal liver enzymes as compared with 14 out of 18 (78%) patients with positive antigenemia (odds ratio=4.77; 95% CI=1.22-20.11; $P = 0.009$). Serum alanine transferase was the most frequently encountered abnormal liver test among those with HBsAg antigenemia occurring in 67% of patients. In 39 patients, serum albumin was measured and was less than the lower normal range in 11 of 18 patients (61%) with positive HBsAg as compared to an abnormally low level in 9 of 21 patients with negative HBsAg (43%). The latter difference was only suggestive, but was not statistically significant. Prolonged prothrombin time was detected in 4 of 9 patients with positive HBsAg and was not measured in any of those with the negative hepatitis marker.

Discussion

Data from different regions of Saudi Arabia have shown that HBV is a highly endemic disease [4-8]. In the present study, chronic HBsAg antigenemia was evident in 6% of 16 apparently healthy Saudi controls. The latter prevalence rate is slightly lower than that commonly reported.

The postulated hypothesis about the high incidence of persistent HBsAg antigenemia among patients with schistosoma mansoni was supported in this case control study. Of those patients with schistosomiasis who tested positive for HBsAG, 23%, 25%, and 28% were Egyptians, Saudis, and Yemeni, respectively. Relative risk analysis has shown that patients with schistosomiasis have a 20% higher risk of being persistent HBsAg carriers than their matched healthy controls.

The high positive rate of HBsAg among patients with schistosomiasis is in keeping with that reported from Egypt. A high prevalence rate of HBsAg has been demonstrated in 50% of children with schistosoma hepatic fibrosis [10]. In another study, 32% of patients with uncomplicated schistosoma mansoni or schistosoma hematobium infections had HBsAg and 40% had anti-HBsAg and/or antibodies against hepatitis B core antigen [11]. Conversely, in another study, the prevalence of anti-HBsAg was 53.7% and 55.2% among cases and controls, respectively [12]. However, in the latter study, controls included patients with "low-grade" schistosoma mansoni infection.

The present data probably supports the association between schistosomiasis and HBV infection for several reasons. First, all our patients had a confirmed diagnosis of schistosomiasis. Second, none of the patients or controls were apparently known to be at any increased risk for acquiring HBV infection including previous blood transfusion. Third, cases and controls were well matched for age, sex, nationality, and place of residence (Saudis only).

The exact mechanism by which patients with schistosomiasis are at higher risk of acquiring HBV infection has yet to be determined. It was recently postulated that HBV infection is probably induced iatrogenically during parenteral treatment of bilharzial patients [11]. Due to the retrospective nature of the study, this suggested mechanism could not be ascertained among our patients.

The contention for mass vaccination against HBV infection for populations living in endemic areas with schistosomiasis has its robust rationale. First, regardless of the mode of transmission, schistosoma patients have a higher risk of acquiring HBV infection. Second, as shown in our data, bilharzial patients with concomitant evidence of persistent HBsAg antigenemia, frequently demonstrate significantly worse liver enzyme levels and probably poorer liver function studies as compared to those without such accompanying viral infection [10,11].

The rationale for mass vaccination of bilharzial patients against HBV infection, however, is precluded by doubts concerning the efficacy of such strategy. On receiving HBV vaccine, schistosomiasis patients showed a diminished response to the vaccine [12,13]. However, both studies included a small number of patients that averts any compelling conjecture. On the other hand, a higher intensified vaccination dose may induce immunity in these patients.

In conclusion, the present case control analysis of the prevalence of HBV infection among patients with schistosomiasis supported the hypothesis that these patients are exposed to a higher risk of acquiring the viral illness. It also appears that these patients are more likely to become chronic carriers for HBsAg once they acquire HBV. The study also showed that a concomitant schistosomiasis and HBV infection has a deleterious effect on patients' liver enzymes and probably function. The preventive role of the dose and frequency of HBV vaccine should be pursued prospectively in a controlled study.

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PREVALENCE OF INTESTINAL PARASITES AMONG EXPATRIATE WORKERS IN AL-AIN, UNITED ARAB EMIRATES

Osama M.G. Ibrahim, MBBCh, MSc,MD; Abdulbari Bener, PhD, FRSS;
Abdulgadir Shalabi, MBBch, DPH

أجريت دراسة مراجعة بين العمال الأجانب في مدينة العين بدولة الإمارات العربية المتحدة لتحديد انتشار الطفيليات الممرضة. اعتمدت الدراسة إلى حد كبير على العمال الأجانب القادمين من الهند، والباكستان وبنغلاديش، وإيران، والفلبين، وسيرلانكا وبعض الأقطار العربية. ويعمل معظمهم أساسًا في مجال تحضير الأغذية، وكخدم في المنازل، ومربيات وكسائقين، تمثل هذه المجموعة نسبة ٤٥,٧٪ من إجمالي عدد الأجانب الجدد القادمين خلال الفترة من ١ يناير ١٩٨٥م إلى ٣١ ديسمبر ١٩٨٨م. تم فحص عينات البراز في ٦٠٢٦٨ فردًا وتبين إيجابية ١٤٠١٠ منهم لوجود طفيليات معوية ممرضة. كانت نسبة انتشار الطفيليات ٢٣,١٪، وجدنا أن أكثر الطفيليات انتشارًا تشمل مايلي: الإنكلوستوما ٦,٧٪، الصفر الخراطيني ٦,٦٪ الدودة السوطية ٦,٢٪ والجياردية اللامبلية ٢,٤. كان توزيع الطفيليات المعوية بين الأجانب مختلفًا لجميع الجنسيات.

أظهرت النتائج أن الجياردية اللامبلية كانت أكثر انتشارًا بين الإيرانيين (٥٤,٧٪) والباكستانيين (٤٢,٢٪) وكانت الإنكلوستوما منتشرة بين السيرلانكيين بنسبة (٣٣,٣٪) والهنود بنسبة (٣٩,٦٪). أما الصفر الخراطيني فكانت منتشرة بين البنغلاديشيين بنسبة (٣٣,١٪) في حين أن الدودة السوطية كانت أكثر انتشارًا بين الفلبينيين.

A retrospective study was conducted among expatriate workers in Al-Ain City, United Arab Emirates (UAE), to determine the prevalence of pathogenic parasitic infestation. The study was based largely on expatriates arriving from India, Pakistan, Bangladesh, Iran, Philippines, Sri Lanka, and other Arab countries and mainly employed as food handlers, housemaids, baby sitters, and private drivers. This group represents 45.7% of the total number of new arrivals of expatriates during the period between 1 January 1985-31 December 1988. Stool specimens were examined in 60,268 screened individuals, of which 14,010 were found to be positive with pathogenic intestinal parasitic disease. Overall parasitic prevelance was 23.1%. The most common parasites found included: *Ancylostoma species* (6.7%), *Ascaris lumbricoides* (6.6%), *Trichuris trichiura* (6.2%), and *Giardia lamblia* (2.4%). The distribution of intestinal parasites among expatriates was different for all nationalities. The results showed that *Giardia lamblia* was more prevalent among Iranians (54.7%) and Pakistanis (42.2%). *Ancylostoma species* was found to be more prevalent among Sri Lankans (33.3%) and Indians (39.6%). *Ascaris lumbricoides* was more prevalent among Bangladeshis (33.1%), and *Trichuris trichiura* was more prevalent among Filipinos (40.2%).

There has been rapid economic growth in the United Arab Emirates (UAE) which has resulted in an enormous increase in the number of expatriate workers. Expatriates in the United Arab Emirates arrive largely from India, Pakistan, Sri Lanka, Philippines, Iran, and other Arab countries. The existence of such workers remaining in the UAE may present a potential health hazard to the local community. Many of these people may be infested with various types of parasites and other bacterial and viral diseases. Moreover, a substantial percentage of expatriates may be carriers of such microbes. The situation is aggravated by the peculiar

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From the Imported Disease Control Centre, Department of Preventive Medicine, Ministry of Health (Dr. Ibrahim), Department of Community Medicine, Faculty of Medicine and Health Sciences, United Arab Emirates University (Dr. Bener), and Director of Preventive Medicine, Ministry of Health, Al-Ain Medical District (Dr. Shalabi), Al-Ain, United Arab Emirates.

Address reprint requests and correspondence to Dr. Bener: Associate Professor, United Arab Emirates University, Department of Community Medicine, Faculty of Medicine and Health Sciences, P.O. Box 17666, Al-Ain, United Arab Emirates.

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type of environmental conditions in which these people live.

The prevalence of almost all intestinal parasites depends on climatic and socioenvironmental conditions. In Saudi Arabia, a neighboring country of the UAE, 7.6% of food handlers working in restaurants located in Dammam and Al-Khobar were found to be infested with parasites and a very low percentage had *Entamoeba histolytica* (3.2%) and *Giardia lamblia* (3.1%) infection [1]. In Yemen, 53% of the stool specimens were found positive for intestinal parasites [2]. The prevalence rate varied in expatriates working in Riyadh, Saudi Arabia [3]; 55.7% of whom were infested with parasites [4]. In another hospital-based study conducted in Riyadh, Saudi Arabia, 22.9% of patients had pathogenic parasites and many more commensals [5]. The prevalence rate of intestinal parasites was found to be higher in expatriates from home countries such as Bangladesh [6], India [7], and Pakistan [8].

In the UAE, all expatriate workers are subjected by law to have clinical examinations and laboratory investigations for various communicable diseases. With the awareness and efforts directed toward control of tropical and communicable diseases, expatriates are required to submit medical examination certificates prior to the start of employment.

However, in the UAE, there remains limited information regarding the epidemiological aspects of parasitic infestation among natives and expatriates. The present study was aimed at determining the current situation of intestinal parasites among expatriate workers in Al-Ain City, UAE, which may reflect a clearer image of the situation in other areas of the country.

Material and Methods

The present study was based on a retrospective survey of intestinal parasitic infestations among expatriates in specific jobs (food handlers, baby sitters, house maids, private cooks, and private drivers) arriving to work in Al-Ain, United Arab Emirates during the period between 1 January 1985-31 December 1988. The age of expatriates ranged from 20 to 45 years. The monthly income of expatriate workers ranged from 400 to 2500 UAE Dirhams (Dh) (1 US $ = 3.68 UAE Dh). Fresh fecal specimens were obtained from 60,286 individuals at the laboratory of Al-Ain Preventive Medicine Department. These specimens were examined by light microscopy of wet smears in normal saline and Lugol iodine solution within one hour of collection [9]. The specimens were received in the laboratory in wide mouth, watertight plastic containers with tightly fitted lids. Periodic random re-examination was carried out throughout the entire period of investigation using the formalin concentration method [10]. Data were entered, recorded, and analyzed on the IBM mainframe of the UAE University. The Statistical Package Program SPSSx was used for statistical computation [11].

Results

The prevalence of various pathogenic intestinal parasitic infestations among expatriates in Al-Ain is shown in Table 1. The overall prevalence was 23.1%. The most common parasites encountered during the period of study were *Ancylostoma species* with a prevalence rate of 6.7%. *Ascaris lumbricoides* ranked second with a prevalence rate of 6.6% followed by *Trichuris trichiura* (6.2%). The least common parasite found was *Entamoeba histolytica* (0.1%). *Ancylostoma species* infection was more common during 1985 and *Ascaris lumbricoides* infection was more common during the period between 1986-1988.

The distribution of parasitic infestations among various nationalities are shown in Figure 1. Sri Lankans represented the majority of positive cases (29.9%) followed by Indians (22.9%), Bangladeshis (20.0%), Filipinos (16.3%), Pakistanis (8.3%), Arabs (8%), Iranians (0.5%), and others (0.2%). The most common parasitic infestations distributed according to nationality in Al-Ain during the period of study are noted in Table 2. The findings revealed that *Giardia lamblia* was more prevalent among Iranians (54.2%), Pakistanis (42.2%), and other Arabs (25.9%). *Ancylostoma species* was more prevalent among Indians (39%) and Sri Lankans (33.3%). *Ascaris lumbricoides* was more prevalent among Bangladeshis (33.1%) and finally, *Trichuris trichiura* was found to be more prevalent among Filipinos (40.2%) and other nationalities (33.3%).

Discussion

The aim of this study was to determine the prevalence rate of intestinal parasitic infestation among new expatriates such as food handlers in Al-Ain, UAE. The overall prevalence rate was 23.1% and the major parasites found were *Ancylostoma species*, *Ascaris lumbricoides*, and *Trichuris trichiura*. The findings demonstrated that there was a gradual decrease in the numbers as well as the prevalence rates for the total intestinal parasitic disease from year to year throughout the period of investigation (1985-1988). These gradual decreases are noted in the *Ancylestoma species*, *Entamoeba histolytica*, and *Hymenolepis nana*. The low prevalence of *Giardia lamblia* and *Entamoeba histolytica* was remarkable. The rates were found to be higher in other Arab countries [1,5]. In addition, the high prevalence rate of intestinal parasites in Bangladesh [6], India [7], and Pakistan [8] are well documented. In southeast Asia, the infestation rate of intestinal parasites was found to be 80.1% in the coastal areas and reached 94.4% in the highland regions [12]. Among Filipinos, the most common parasites found were *hookworms* 44%, *Schistosoma japonicum* 16%, and *Trichuris trichiura* 12% [13]. In studies conducted on expatriates living in Saudi Arabia, 55.7% revealed single-parasite infestations and 10.5% of the expatriate population were found to

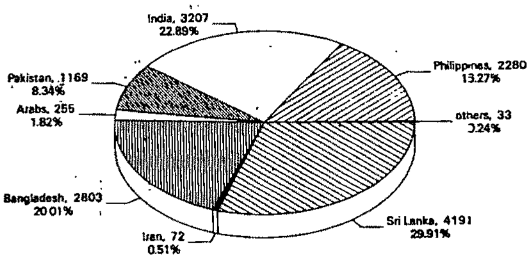

FIGURE 1. Distribution of intestinal parasites among various nationalities from 1985-1988 in Al-Ain, United Arab Emirates (UAE).

TABLE 1. *Prevalence of common parasitic infections among expatriates in Al-Ain, United Arab Emirates (UAE).*

Years	*Giardia lamblia*	*Entamoeba histolyca*	*Ancylostoma duodenale*	*Ascaris lumbricoides*	*Trichuris trichiura*	*Hymenolepis nana*	Other intestinal parasites	Total
1985	3.7%	0.2%	9.9%	7.9%	7.7%	0.7%	1.5%	31.6%
1986	2.0%	0.2%	7.9%	9.0%	8.0%	0.2%	0.8%	28.1%
1987	1.8%	0.1%	6.1%	5.6%	6.6%	0.2%	0.5%	20.9%
1988	2.5%	0.1%	4.1%	4.9%	3.4%	0.1%	0.3%	15.4%
1985 to 1988	2.4%	0.1%	6.7%	6.6%	6.2%	0.3%	0.7%	23.1%

TABLE 2. *Comparison of common parasitic infections distributed according to nationality in Al-Ain, United Arab Emirates (UAE).*

Nationality		*Giardia lamblia*	*Entamoeba histolyca*	*Ancylostoma duodenale*	*Ascaris lumbricoides*	*Trichuris trichiura*	*Hymenolepis nana*	Other intestinal parasites	Total
Indian	*	375	9	1271	809	575	33	135	3207
	**	11.7%	0.3%	39.6%	25.2%	17.9%	1%	4.2%	100%
Pakistani	*	493	31	20	244	97	104	53	1169
	**	42.2%	2.6%	17.2%	20.9%	8.3%	8.9%	4.5%	100%
Filipino	*	125	9	383	812	916	4	31	2280
	**	5.5%	0.4%	16.8%	35.6%	40.2%	0.2%	1.4%	100%
Bangladeshi	*	220	11	762	929	760	4	117	2803
	**	7.9%	0.4%	27.2%	33.1%	27.1%	0.1%	4.2%	100%
Sri-Lankan	*	209	19	1396	1140	1368	8	55	14010
	**	5%	0.4%	33.3%	27.2%	32.6%	11.1%	1.3%	100%
Iranian	*	39	2	8	5	3	14	4	72
	**	54.2%	2.8%	11.1%	11.1%	4.2%	5.5%	5.5%	100%
Arab countries	*	66	5	39	57	24	2	50	255
	**	25.9%	2%	15.3%	22.3%	9.4%	6.1%	19.6%	100%
Others	*	1	0	5	11	12	2	2	33
	**	3%	0	15.1%	33.3%	36.4%	6.1%	6.1%	100%
Total	*	1474	86	4065	4010	3755	173	447	14010
	**	10.5%	0.6%	29%	28.6%	26.8%	1.2%	3.2%	100%

* Numbers of recorded cases.
** Percentage of infecton.

be infested by more than one parasite [14]. Among the Saudi population, the prevalence rate was found to be comparatively low at 9.3% [3] and prevailing parasites were *Giardia lamblia, Schistosoma mansoni,* and *Entamoeba histolytica* [15]. But in the southern region of Saudi Arabia there was a relatively low infestation rate with intestinal parasites [16]. In the western region of Saudi Arabia, *Entamoeba histolytica* was found in 9.6% of the stool samples examined, followed by *Giardia lamblia* at 4.5% [17]. A study recently conducted by Ali et al [8] in Medina demonstrated that approximately 14% of 13,216 individuals harbored potentially pathogenic parasites in which the most common parasite was *Giardia lamblia* (33%) and the highest incidence of parasitic load was found to be among Sri Lankans (40.7%) [18].

In the present study, we obtained a relatively low prevalence rate of intestinal parasites among expatriates working in the UAE when the results were compared with the expatriates' home countries [6-8,12]. However, this may be attributed to the concept that the UAE is considered to be an enticing place to work for workers seeking to improve their personal living conditions, especially those coming from socioeconomically poor countries. For these workers, the competition for employment is high, with employers selecting only the healthiest employees. Moreover, all expatriates have been subjected to medical examinations and laboratory investigations in their home countries prior to their arrival in the UAE.

In conclusion, the present investigation demonstrates that the infestation rate remains a compromising health problem, especially when it has been noted that 96.8% of all detected types of parasites are transmissible and could easily be transmitted without the need of the vectors of transmission, animal reservoir hosts, or animate or mobile intermediate hosts. The highest prevailing parasites *(Ancylostoma species, Ascaris lumbricoides* and *Trichuris trichiura)* representing 84.4% of all positive cases are defined as "geohelminths." All that is needed for transmission is inanimate soil [19]. Other less frequent parasites *(Giardia lamblia, Entamoeba histolytica and Hymenolepis nana)* are known to be infective through fecal-oral route. Thus, the actual possibility of spreading such diseases throughout the community may be a potential risk. It is recommended that expatriate workers be checked and treated if necessary on arrival in the UAE and examined upon returning from their annual home leave vacations. This policy must be strictly monitored, particularly for caterers and domestic workers.

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PATERNAL LEUKOCYTE IMMUNIZATION IN PRIMARY RECURRENT SPONTANEOUS ABORTERS

Ahmed M. Bahar, FRCOG: Arthur G. White, PhD;
Ismail H. Al-Abdullah, PhD

أجريت هذه الدراسة المبدئية لتقصي الأدوار المحتملة لمستضد الكريات البيضاء الآدمية والأضداد السامة لخلايا الأب اللمفية والأضداد التابعة للوالدة والمحصرة لتفاعل اللمفيات المختلطة لخلايا الأب في المحافظة على الحمل عقب تحصين المريضات اللواتي أصبن بإجهاض متكرر بكريات الدم البيضاء الأبوية. تم استقصاء ما مجموعه ٣٦ مريضة عانين من إجهاض تلقائي أولي متكرر وغامض في الثلث الأول من الحمل وذلك لاكتشاف تلك الأضداد. كانت نسبة الاختلاف من حيث وجود الضدين ٤٣,٣٪ $P<$ ٠,٠٥ تم التحصين بكريات الدم البيضاء الأبوية في مناسبتين لدى مامجموعه ٢٦ مريضة من اللاتي يفتقرن لأي من الضدين، وأعيدت المقايسات بعد التحصين. كان معدل التحول المصلي ٥٠٪ للأضداد السامة للخلايا اللمفية و ٦١,٥٪ للأضداد التابعة للأم والمحصرة لتفاعل اللمفيات المختلطة. تحقق الحمل لدى عشرين (٢٠) مريضة بعد التحصين، وأكملت إحدى عشرة (١١) منهن الحمل بنجاح، بينما تكرر الاجهاض لدى التسع (٩) الأخريات اللاتي أخفق لديهن التحويل المصلي. في حين تكرر الإجهاض لدى المريضات الأخريات كن الحمل ناجحًا لدى مامجموعه ٨٣,٣٪ من المريضات اللواتي أنتجن الأضداد المحصرة لتفاعل اللمفيات المختلطة بعد التحصين في حين تكرر الإجهاض لدى المريضات الأخريات اللاتي أخفق لديهن التحويل المصلي. ويعتبر هذا الفرق ذا أهمية إحصائية (nP٠٥) كان الحمل ناجحًا أيضًا بعد التحصين لدى مامجموعه ٥٠٪ من المريضات اللواتي أنتجن أضدادا سامة للمفيات، بينما تكرر الاجهاض لدى ٤٠٪ فقط من المريضات اللاتي أخفق لديهن التحويل المصلي. شعرنا أن هذا الفرق ليس ذا أهمية إحصائية. إن إنتاج الأضداد المحصرة لتفاعل اللمفيات المختلطة بعد التحصين يعتبر مؤشرًا أفضل على نجاح الحمول القادمة إذا قورن بإنتاج الأضداد السامة للخلايا اللمفية.

This was a pilot study to investigate the possible roles of human lymphocyte antigen (HLA), antipaternal lymphocytotoxic antibodies, and maternal antipaternal mixed lymphocyte reaction (MLR) blocking antibodies in the maintenance of pregnancy following paternal leukocyte immunization for patients with recurrent abortions. A total of 36 patients with unexplained, first trimester, primary recurrent spontaneous abortions were investigated for the detection of these two antibodies. There was a 43.3% rate of discordance in the presence of the two antibodies ($P < 0.05$). A total of 26 of these women who lacked either antibody were immunized with paternal leukocytes on two occasions and the assays were repeated post-immunization. The seroconversion rate was 50% for lymphocytotoxic antibodies and 61.5% for maternal serum (MLR) blocking antibodies. Twenty patients achieved pregnancies post-immunization, 11 completed their pregnancies successfully, and 9 re-aborted. A total of 83.3% of patients who developed MLR blocking antibodies post-immunization had successful pregnancies while those who failed to seroconvert aborted again. This difference is statistically significant ($P < .05$). A total of 50% of patients who developed lymphocytotoxic antibodies post-immunization had successful pregnancies while only 40% who failed to seroconvert re-aborted. This difference, we felt, was not statistically significant. The development of MLR blocking antibodies post-immunization is a better indicator of subsequent successful pregnancies than lymphocytotoxic antibodies.

From the Department of Obstetrics and Gynecology (Dr. Bahar), and the Department of Organ Transplantation (Drs. White and Al-Abdullah), Faculty of Medicine, University of Kuwait.

Address reprint requests and correspondence to Dr. Bahar: King Saud University, Abha Branch, College of Medicine, P.O. Box 641, Abha, Saudi Arabia.

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Certain instances of unexplained spontaneous abortions may be due to the failure of immunological recognition and adaptation to the fetoplacental unit. The precise nature of this interaction is not completely understood; however, one feature may be the failure of the fetus to stimulate in the mother protective antibodies that alter antigen expression as well as promote growth of the trophoblast [1,2].

Treatment by immunization with paternal or donor leukocytes to stimulate antibody production to leukocyte trophoblast crossreactive epitopes has been tried by different groups with encouraging results [3]. In these groups, the criteria for selection of patients for immunotherapy differ. One criterion is the sharing of HLA antigens [4]. There is evidence of increased antigen sharing between recurrently aborting women and their partners with sharing frequencies more than can be expected by chance alone [5-7]. Other criteria include the lack of paternal HLA lymphocytotoxic antibodies [8-10] or the lack of mixed lymphocytic reaction (MLR) blocking antibodies [11-13]. These antibodies are commonly present in the sera of normal multiparous women but found to be lacking in the sera of recurrently aborting women [14-20].

The results of immunotherapy on successful pregnancy outcome using different criteria for selection are quite similar [3]. One may expect better results if the criteria for immunization were standardized. However, the crossmatch test to detect cytotoxic antibodies is simpler and cheaper than the blocking of MLR assay for the detection of blocking antibodies. This may be the reason why in most studies the sole criterion for selection of patients for immunotherapy is the lack of cytotoxic antibodies. In the present study, women were selected for immunotherapy if they lacked either lymphocytotoxic or MLR blocking antibodies or both in a trial to determine whether these antibodies correlate in any way with the outcome of a subsequent pregnancy.

Patients and Methods

A total of 36 women who attended our recurrent pregnancy loss clinic with three or more documented recurrent first trimester abortions and no living children were selected for immunological investigations. The mean age was 27 ± 3.9 and the mean number of previous abortions was 4.25 ± 1.5. Other possible etiologies of recurrent pregnancy loss (i.e., anatomical, infectious, chromosomal, metabolic, endocrine, or autoimmune disorders) were excluded. These were excluded by clinical examination and the following investigations were performed: midluteal progesterone level, serum prolactin level, thyroid function test, fasting blood sugar, cervical swab for culture of listeria and detection of chlamydia, karyotyping of the couples, activated partial thromboplastin time (APTT), VDRL, antinuclear factor and immune complex, and hysterography. Serum anticardiolipin antibodies were measured after the patients received immunotherapy, as this was not previously available. All women had experienced their last miscarriage within the prior year. An informed consent for immunization was obtained from each patient and her consort after approval from the human ethical committee. The serum of all women was tested for the presence of anti-paternal T&B lymphocytotoxic antibodies using the standard National Institute of Health (NIH) crossmatch test [21]. In 30 women, maternal serum MLR blocking assays were carried out for the detection of MLR blocking antibodies. Women found to be lacking one or both antibodies were immunized with paternal leukocytes after the husband's blood proved negative for hepatitis B antigen and HIV antibodies. The women were immunized on two occasions in intervals of six weeks. One month following the second immunization, the tests were repeated and the patients were requested to establish a pregnancy irrespective of the results of the tests. The McNemar test was used to assess the difference in antibody frequency preimmunization between the MLR and the crossmatch tests. The Fisher exact test was used to assess the difference in antibody production between successful and unsuccessful pregnancies post-immunization with paternal leukocytes.

Lymphocytes Crossmatching: (Crossmatch test)

Standardized lymphocyte crossmatching using the microcytotoxicity assay [21] was carried out between the wife's serum and the husband's lymphocytes as follows: Lymphocytes were separated from 10-15 ml of defibrinated blood using a density gradient medium, washed with tissue culture medium and resuspended at $2x10^6$ ml in medium. An aliquot of cells was used in a "total" crossmatch using serum from the wife's undiluted and diluted at 1/2, 1/4, and 1/8 as well as negative and positive control sera. Autologous crossmatch using the cells from the wife was included. One microliter of the lymphocyte suspension was added to 1 µl of serum and incubated for one hour at room temperature prior to the addition of 5 µl of rabbit complement and a further two hour incubation. The reaction was stained with eosin and fixed with formalin before scoring the percentage kill. A positive reaction was interpreted as a kill of 20% or greater than the autologous/AB controls.

The remaining lymphocytes were separated in T&B cells on a nylon wool column [22] prior to repeating the crossmatch procedure using these cell suspensions. For T lymphocytes, incubation was at room temperature for 30 minutes prior to the addition of rabbit complement and then a further one hour incubation. For B lymphocytes, the initial incubation was one hour at 37°C followed by incubation for two hours at room temperature.

Mixed Lymphocyte Culture Reaction Assay (MLR)

The principle and the methodology of this assay have been described in the literature [23]. The changes in the assay described here are to investigate the serum of the wife for its ability to inhibit the MLR against the husband's cells.

Sixty ml of blood were drawn from the wife, 30 ml for serum separation and 30 ml for lymphocyte separation. Thirty ml of blood were drawn from the husband for lymphocyte separation. Lymphocytes were isolated using the same method utilized for lymphocyte crossmatching. Responding lymphocytes were used at $1x10^6$/ml with $3x10^6$/ml mitomycin-treated stimulating cells and cultured in medium 199, containing bicarbonate, penicillin/streptomycin and either 20% heat inactivated (56°C for 30 minutes) pooled AB serum or 20% heat inactivated wife's serum. The reaction was carried out in flat bottom microplates with mylar seals using 125 µl aliquots of responding or stimulating cells in a one-way reaction. All reactions were carried out in triplicate. The plates were incubated for four days at 37°C in a humidified incubator. After the incubation, 1 µc of tritiated thymidine (TRK61 Amersham International, UK) was added to each well and reincubated for 24 h prior to harvesting the cells. Assessing the incorporated radioactivity was performed by using a liquid scintillation spectrometer. The results were expressed as a stimulation index between the wife's responding cells and the stimulating cells of the husband. The MLR blocking activity was estimated by dividing the response in the wife's serum by that in the pooled AB serum. A reduction of 50% or more compared to the response in pooled AB serum was considered as evidence of blocking activity.

Crossmatching and the MLR blocking assay were performed prior to and after leukocyte immunization.

Leukocyte Preparation and Immunization

A leukocyte-rich blood concentrate was isolated from 500 ml of blood using a cell separator machine (Hemonetics V50 pheresis system). After mononuclear cell separation, the blood was transfused back to the donor using a closed circuit system. The lymphocytes were separated by lymphoprep gradient and centrifugation, washed three times in Hartman's solution and finally suspended in 5 ml of saline. Three ml of cell suspension were injected intravenously, 0.5 ml of cell suspension were injected subcutaneously and intradermally at two sites on the forearm. A total of $150x10^6$ through $400x10^6$ leukocytes were given to each patient.

Results

The results of the crossmatch and MLR tests prior to immunization are shown in Table 1. In the 30 patients in whom both tests were carried out, it was found that there was a 43.3% rate of discordance between the two tests in the presence of antibodies. This difference in antibody frequency was statistically significant ($P < 0.05$) (Table 2).

Among the 36 patients, 26 patients received leukocyte immunization. A total of 12 out of 24 patients who were initially crossmatched negative developed antipaternal cytotoxic antibodies following leukocyte immunization (seroconversion rate; 50%). All patients who seroconverted developed antibodies for both T&B lymphocytes except one patient who developed antibodies for B lymphocytes only. Eight out of 13 patients who were initially MLR negative developed MLR blocking antibodies after the leukocyte immunization (seroconversion rate 61.5%).

Thus far, 20 patients have achieved pregnancy following leukocyte immunization. All of these patients had a crossmatch test prior to and following immunization, but only ten had MLR assays prior to and following immunization. Eleven patients had successful pregnancies and nine patients re-aborted. The overall success rate was 55%. All of the deliveries were normal except two patients who were delivered by cesarean section at term; one because of triplets and the other because of failure to progress during labor. There were no infants with congenital abnormalities or growth retardation.

Among the nine patients who re-aborted, four miscarried during the second trimester at 20, 22, 18, and 19 weeks' gestation, respectively. Two of these were missed abortions and the other two were fresh abortions. No congenital abnormality was found in any fetus on autopsy. One of the fresh abortions (No. 3) occurred following bleeding of several days' duration from a low lying placenta. The antibody status of these patients is shown in Table 3.

TABLE 1. *Crossmatch and MLR tests before immunization.*

Test	Negative	Positive	Total
Crossmatch	30	6	36
MLR	15	15	30

TABLE 2. *Correlation between MLR and Crossmatch tests in 30 patients.*

Both tests positive	4	13.3%	56.7 %
Both tests negative	13	43.4%	
MLR positive and Crossmatch negative	11	36.7%	43.3%
MLR negative and Crossmatch positive	2	6.6%	

The difference in antibody frequency is significant McNemar's test: $P<0.05$.

Table 4 shows the relationship of the development of lymphocytotoxic antibodies and MLR blocking antibodies to the pregnancy outcome. Five out of six patients who developed MLR blocking antibodies post-immunization had successful pregnancies with a success rate of 83.3%. The other four patients who failed to seroconvert re-aborted during the first trimester of pregnancy. This difference in the development of MLR blocking antibodies between successful and unsuccessful pregnancies was statistically significant ($P < 0.05$). In contrast, 5 out of 10 patients who developed lymphocytotoxic antibodies post-immunization achieved successful pregnancies with a success rate of 50% while only 4 out of 10 patients who failed to seroconvert re-aborted. The difference in the development of lymphocytotoxic antibodies between successful and unsuccessful pregnancies was found to be insignificant.

The results of anticardiolipin antibody assay performed later post-immunization showed weak positive results in two patients and a strong positive result in one patient. Both patients with weak positive results delivered successfully at term. The patient who demonstrated a strong positive result re-aborted during the first trimester of pregnancy. This patient was MLR positive prior to immunization.

TABLE 3. *Antibody status of patients who aborted during the second trimester of pregnancy.*

		Antibody Preimmunization		Antibody Postimmunization		
	Gestation (weeks)	Cytotoxic	MLR blocking	Cytotoxic	MLR blocking	Type of Abortion
1	20	Negative	Positive	Positive	Positive	Missed
2	22	Negative	Positive	Negative	Positive	Missed
3	18	Negative	Negative	Positive	Positive	Fresh
4	19	Negative	Not done	Negative	Negative	Fresh

TABLE 4. *Pregnancy outcome postimmunization in relation to the development of lympocytotoxic and MLR blocking antibodies.*

	Lymphocytotoxic antibodies (n=20)				MLR blocking antibodies (n=10)			
	Positive		Negative		Positive		Negative	
Outcome	n	(%)	n	(%)	n	(%)	n	(%)
Successful	5	(50)	6	(60)	5	(83)	0	(0)
Abortion	5	(50)	4	(40)	1	(17)	4	(100)
Total	10	(100)	10	(100)	6	(100)	4	(100)

Discussion

The results of this study demonstrated that the relationship between the presence of HLA antipaternal cytotoxic antibodies and MLR blocking antibodies preimmunization is not strong, suggesting that these antibodies recognize different antigens, and that the development of the MLR blocking antibodies post-immunization is a better predictor in determining the success of immunization leading to successful pregnancy. The finding that only 50% of patients who developed lymphocytotoxic antibodies had successful pregnancies while successful pregnancies were also achieved in 60% of patients in spite of their failure to develop these antibodies raises the question of the lack of association between anti-paternal cytotoxic antibodies and subsequent pregnancy outcome. In a prospective study of spontaneous abortion conducted in Cambridge, England, Regan [24] reported that only 38% of women who had a live birth ever produced detectable cytotoxic antibodies and that the majority of positive results were found only after the pregnancy had reached the third trimester. Only 4 out of 120 women who had live births developed antibodies prior to 14 weeks' gestation. The lack of correlation of cytotoxic antibodies with pregnancy outcome post-immunization was also reported by other investigators [11,25]. However, others reported that cytotoxic antibodies are predictive of favorable pregnancy outcome [8-10]. However, these investigators did not include MLR blocking assays in their studies.

Although the results of this study indicate that MLR blocking antibodies remain a more reliant predictor of a subsequent successful pregnancy, it does not indicate that they are solely responsible for the maintenance of pregnancy. There are undoubtedly other factors which are immunoregulatory during pregnancy. Among these are the presence of T suppressor cells [3], anti-FC receptor antibodies [26] and anti-idiotypic antibodies [27]. The presence of MLR inhibiting activity in the serum as a more reliant indicator of a successful outcome post-immunization has been noted in the literature [11,12].

In this study, seven patients who were initially having MLR blocking antibodies preimmunization were immunized. Four of these patients achieved pregnancy, one completed the pregnancy satisfactorily while the other three re-aborted. Each patient proceeded to 12, 20, and 22 weeks, respectively for the first time, but aborted. One wonders whether this was due to the effect of immunization that was reached at this stage of pregnancy or that immunization was found to be harmful. One patient has again become pregnant and her pregnancy is 35 weeks advanced and progressing normally. She did not receive any further immunization following her previous abortion. The patient who aborted at 12 weeks' gestation was found later to have a high level of anticardiolipin antibodies in her serum. She achieved another pregnancy and is now 28 weeks pregnant. Her pregnancy is, at present, progressing normally. This patient was prescribed aspirin and heparin treatment at the beginning of this pregnancy. Unander and Lindholm [12] reported five patients who miscarried again after receiving immunization. They were intially MLR blocking antibody positive and four showed autoantibodies as signs of autoimmune disease. Although we did not detect signs of autoimmune disease in our patients, the finding of high serum anticardiolipin antibodies in one patient gives sufficient warning to be careful in patient selection. This preliminary study suggests that the inclusion of MLR blocking assay in the evaluation of patients with unexplained recurrent abortions is essential for patient selection prior to considering immunotherapy. We also recommend that tests for antiphospholipid antibodies be performed.

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CHILDHOOD IDIOPATHIC THROMBOCYTOPENIC PURPURA: EXPERIENCE AT KING KHALID UNIVERSITY HOSPITAL, RIYADH

Ibrahim M. Al Fawaz, MBBS, FAAP, FRCP(C)

أجريت دراسة استطلاعية لحالات ٤٩ طفلاً (٣٠ ذكورًا و ١٩ إناثًا) يعانون من فرفرية قلة الصفيحات الغامضة، كانوا قد شوهدوا في مستشفى الملك خالد الجامعي خلال فترة سبع سنوات ونصف السنة، وذلك فيما يتعلق بالخصائص السريرية والمعالجة ونتائج العلاج. تراوح سن بداية المرض بين ثمانية شهور وأحد عشر عامًا وكان المتوسط ٤,٢٦ سنة. راجع سبعة وعشرون طفلاً المستشفى وهم يعانون من فرفرية نقص الصفيحات الغامضة المزمنة. كانت السمات السريرية الإمراضية والاستجابة للعلاج مماثلة بصفة أساسية للمشاهدات في أنحاء أخرى من العالم. وفي البحث عن مؤشر على إزمان المرض اتضح أن عدّ الصفيحات بعد أربعة أسابيع وثلاثة شهور من التشخيص يشكل عاملاً هامًا في التكهن بإزمان فرفرية قلة الصفيحات الغامضة. فإذا كان عدد الصفيحات أقل من ١٠٠ × $١٠^{٩}$/ل في هذه الفترات ازداد خطر إزمان المرض والعكس بالعكس. من ناحية ثانية لم يكن هناك ترابط بين مدة الأعراض قبل مراجعة المستشفى ومآل المرض خلافًا لما ورد في تقارير الباحثين من أوروبا واستراليا.

Forty-nine children (30 boys and 19 girls) with idiopathic thrombocytopenic purpura (ITP) seen at King Khalid University Hospital (KKUH) Riyadh, during a 7-1/2 year period were retrospectively reviewed with regard to their clinical characteristics, management, and outcome. The age of onset of the disease ranged from 8 months to 11 years with a mean of 4.26 years. Twenty-seven cases presented as acute ITP while 22 cases presented as chronic ITP. The clinicopathological features and response to treatment of the cases were essentially similar to findings in other parts of the world. In a search for a predictor of chronic disease, the platelet counts at four weeks and three months after diagnosis were found to be a significant factor for prediction of chronicity of ITP. If the platelet counts are less than 100×10^9/L during these periods, the risk of chronic ITP is increased and vice versa. There was, however, no correlation in our patients between duration of symptoms prior to presentation and outcome of the disease as has been reported by investigators in Europe and Australia.

Idiopathic thrombocytopenic purpura (ITP) in children is usually a brief, self-limiting disease with a low morbidity and mortality [1-4]. However, 10-30% of children may fail to achieve sustained remission [1-5], and in such cases, ITP runs a prolonged course with platelet counts fluctuating in response to infections, steroid therapy, gammaglobulin infusions, splenectomy, and other factors. The disease has, therefore, been traditionally divided into the acute and chronic types depending on the duration of documented thrombocytopenia and children whose thrombocytopenia persists for more than six months classified as chronic ITP [6,7]. The long-term prognosis of ITP in childhood is usually benign [4,8,9], but there is a small risk (<1-4%) of intracranial hemorrhage [4,10,11] which may necessitate continuous medical follow-up and, at times, restriction of physical activities.

Several recent reports, particularly from North America, Europe, and Australia [8,12,13], have shown that certain characteristics of some ITP patients at presentation and their patterns of recovery of platelet counts after diagnosis, constitute predictors or risk factors for the development of chronic ITP. The clinicopathological features and prognosis of childhood ITP in Saudi Arabia have not been delineated. The purpose of this retrospective study therefore is to report our experience with

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From the Department of Pediatrics, College of Medicine, King Saud University, Riyadh.

Address reprint requests and correspondence to Dr. Al Fawaz: King Saud University, Department of Pediatrics (39), College of Medicine, P.O. Box 2925, Riyadh 11461, Saudi Arabia.

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childhood ITP, which is, to our knowledge, the first report on this condition from Saudi Arabia.

Material and Methods

The case files of 56 children identified as having idiopathic thrombocytopenic purpura at King Khalid University Hospital (KKUH), Riyadh, Saudi Arabia from June 1983 to December 1990 were reviewed and constitute the material for this study. A total of seven cases among the 56 children were excluded from the present analysis. Two patients were excluded because of inadequate follow-up following discharge from the hospital, while the remaining five did not satisfy the criteria for the diagnosis of ITP; among these, thrombocytopenia was secondary to malaria in one case, familial in three other cases, and neonatal in the fifth case. In the 49 study cases, the diagnosis of ITP was based on a platelet count of less than $100x10^9/L$, an adequate or increased number of megakaryocytes in the bone marrow, and absence of identifiable systemic disease or other hematologic abnormalities together with a history of increased bruising, petechiae and/or mucous membrane bleeding. Coomb's test, liver function tests, antinuclear antibodies, monospot test and/or EB virus serology were performed on all patients. Platelet count, hemoglobin, hematocrit, white blood count, and differential were obtained from the patient at each clinic visit. The following information about each patient was obtained: age, sex, season of onset of symptoms, the duration and nature of symptoms and signs at initial presentation to KKUH or the referring hospital, history of viral illness during the four weeks prior to the onset of symptoms, complications, sequential platelet counts, treatment, and outcome. Each patient was categorized as acute or chronic, the latter being defined as persistent or recurrent thrombocytopenia (platelet count less than $100x10^9/L$ for more than six months after presentation).

For statistical analysis, chi-square and Fisher exact tests were used and *P* values less than 0.05 were considered statistically significant. Also, sensitivity, specificity, and predictive values were calculated according to standard statistical methods [14].

Results

The 49 study cases consisted of 30 boys and 19 girls; 41 were Saudi nationals and eight were non-Saudi nationals. The age of onset of ITP ranged from eight months to 11 years, with a mean of 4.26 years. Some characteristic features of the acute and chronic cases are compared in Table 1. There were 27 cases classified as acute ITP and 22 cases classified as chronic ITP, respectively. There were no clear-cut differences in seasonal distribution of the cases although more than 60% of the total occurred during the winter and spring seasons. Also, the acute and chronic ITP cases occurred equally throughout the year. Proceeding infection occurred in only 18 patients (36.7%) and in all of these, respiratory tract infections were incriminated. The duration of symptoms prior to presentation was similar in the chronic and acute groups. Among the 22 chronic ITP cases, there were 13 cases (7 boys and 6 girls) who were referred to KKUH after diagnosis of ITP for a second opinion or for surgery. The mean follow-up time for the patients with acute

TABLE 1. *Comparison of characteristic features between 27 children with acute ITP and 22 children with chronic ITP.*

Patients' Characteristics	Acute		Chronic	Total
	27		22	49
Sex				
Male	18		12	30
Female	9		10	19
	chi-square	=	0.7502	
	P	=	0.3864	
Age (yrs)				
0.5 - 3 yrs	15		7	22
4 - 7 yrs	9		14	23
8 - 11 yrs	3		1	4
	chi-square	=	4.5330	
	P	=	0.1037	
Viral illness 4 weeks prior to onset				
Yes	15		3	18
No	12		19	31
	chi-square	=	9.1659	
	P	=	0.0025	
Seasonal onset				
Winter	5		10	15
Spring	10		5	15
Summer	7		3	10
Autumn (Fall)	5		4	9
	chi-square	=	4.5819	
	P	=	0.2051	
Duration of symptoms prior to presentation				
≤ 2 weeks	18		12	30
> 2 weeks	9		10	19
	chi-square	=	0.7502	
	P	=	0.3864	

disease was 13.8 months after platelet counts returned to normal (range 2-48 months). In contrast, the chronic patients were followed up for extended periods, mostly for longer than three years except in seven children among the referral group who were followed up for only 1 to 1-1/2 years following diagnosis. Among the children with chronic ITP who were followed for longer periods of time, ten patients (66.7%) remained thrombocytopenic for more than two years after diagnosis. Five out of these ten cases had a spontaneous remission during the follow-up at 2 years and 9 months in one, 3 years in two, 5 years in one, and 7 years in another.

Among the cohort of 36 cases who were initially seen at KKUH, 27 cases (75%) had acute ITP and nine cases (25%) had the chronic type disease. The platelet counts for these 36 cohort cases at four weeks and three months are shown in Table 2, together with their outcome. There was a statistically significant association between chronicity of disease and platelet counts as indicated by chi-square test ($P < 0.05$). The platelet count was further collapsed into the dichotomous group high and low (where high is defined as a platelet count of more than 100×10^9/L) and noted in Table 2. The sensitivity, specificity, and positive predictive values of platelet counts at four weeks were 77.8% and 91.3%, respectively. At three months, the sensitivity and predictive values increased to 85.2% and 92%, respectively while the specificity remained at 77.8%. Therefore, the risk of chronicity is high when platelet counts are less than 100×10^9/L at 28 days and three months following diagnosis.

TABLE 2. *Platelet counts at four weeks and three months in the 36 patients with ITP seen initially at KKUH.*

Platelet Counts	Chronic (n=9)		Outcome	
			Acute (n=27)	Total (n=36)
4 weeks ($\times 10^9$/L)				
< 50	4		4	8
50 - 100	3		2	5
< 150	1		10	11
> 150	1		11	12
	chi-square	=	9.1960	
	P	=	0.0268	
3 months ($\times 10^9$/L)				
< 50	2		2	4
50 - 100	5		2	7
< 150	1		1	2
> 150	1		22	23
	chi-square	=	15.2795	
	P	=	0.0016	
6 months ($\times 10^9$/L)				
< 50	7		0	7
50 - 100	2		0	2
< 150	0		8	8
> 150	0		19	19
	Fisher's Exact	=	$P<0.001$	

The chi-squared analysis also revealed that duration of symptoms is not statistically significantly associated with chronicity of the disease ($P > 0.1$). However, there was a significant association between viral illness at four weeks prior to onset and disease chronicity ($P < 0.01$). A low proportion of the chronic cases had no history of preceding viral illness.

Treatment

In the acute ITP group, 12 cases received no treatment, 14 received steroids (prednisolone starting with 2 mg/kg/day for 2-4 weeks and then tapered) and two patients received gammaglobulin (0.4-0.8 g/kg/dose) for five days; one patient received it in addition to steroid and the other without steroids. In the chronic group, all 22 cases received steroid therapy sometime during the course of their disease; 12 were steroid-resistant and 10 were steroid-dependent; 18 chronic patients also received multiple two or five day courses of intravenous gammaglobulins (0.4-0.8 g/kg/dose). The peak elevation in platelet count occurred around 4-7 days following initial gammaglobulin treatment and was more than 150×10^9/L in seven cases, between 50-100×10^9/L in another seven cases, and between 30-50×10^9/L in four cases. Subsequently, three patients did not respond to further treatment; nine patients maintained platelet counts at $>30 \times 10^9$/L without further treatment and six patients required booster infusions of gammaglobulin every 4-8 weeks to maintain a platelet count at $>30 \times 10^9$/L.

In the chronic group, five patients underwent splenectomy approximately one year following diagnosis (average 16.8 months, range 12-24 months). The splenectomies were performed electively and there were no postoperative complications or long-term complications such as septicemia after a mean follow-up of 16.4 months (range 4-48 months). The ITP resolved in only three patients following splenectomy.

Presentation and Hospital Course

All patients initially presented with petechiae and ecchymoses. Twenty-three patients had mild to moderately severe epistaxis. Blood transfusions (packed RBCs) were given in less than 10% of the cases. Intercurrent viral infections were found to be associated with about 25% of the episodes of recurrent ITP. One patient, an eight-month-old boy from the acute ITP group, sustained a fall from his crib and developed subdural hematoma which was successfully evacuated surgically. He received steroid therapy and platelet transfusions (before the gammaglobulin therapy era) and the patient's platelets eventually returned to normal range.

Discussion

The main clinicopathological features of idiopathic thrombocytopenic purpura in Saudi Arabian children, as described in the present study, are similar to those reported from other parts of the world with some slight differences [1-12]. The inclusion in our total study population of referred chronic patients resulted in a selection bias toward the chronic ITP cases. But, when the ITP cases which were seen initially at KKUH were analyzed separately, there were only 9 out of 36 cases (25%) persisting more than six months after diagnosis. This percentage of chronic ITP cases is similar to figures from Europe, Australia, and North America [1,2,4,8,12,16]. In this series, there was a preponderance of males over females with a ratio of 3:2 for acute ITP cases. This figure was not biased by the addition of the referred cases because the number of males and females were almost equal in this group. However, we are unable to explain this sex difference because in other series, there was no sex difference in acute ITP in childhood [1-5,7,12]. While the age of onset is quite variable, the peak age in our study was 2-5 years, which is also the peak age of viral infections, very similar to the findings in several reports [1-5,8,12,15]. We also concur with Lusher and Iyer [15] and Choi and McClure [16] in the observation that the frequency of chronic disease is uniform throughout all age groups of children. However, because we had very few patients older than ten years of age, we were unable to draw any conclusions for this age group in terms of chronicity of the disease. There was no clear-cut seasonal distribution in our patients; however, the majority of cases occurred during the winter and spring months which remain the most common seasons for viral infections [4,15]. There were no fatalities in this series; however, one patient developed intracranial hemorrhage (ICH) secondary to head injury and recovered following treatment. Intracranial hemorrhage is a well recognized complication of ITP and has been reported to occur in less than 1-2% of patients [4,10,11]. Analysis of all reported cases of ICH in childhood ITP revealed that all the children had a platelet count of less than $20\times10^9/L$ at the time of hemorrhage and there was no obvious "high risk time" for ICH [4,11]. The mortality in all recent series has been in the range of 0-1% with an overall frequency of 0.43%[4].

It is generally agreed that the use of corticosteroids does not alter the ultimate course of ITP [2,5] and splenectomy has been recommended if spontaneous remission does not occur within six months or one year following diagnosis [3,6-8,15]. Remission following splenectomy in this study occurred in three out of five cases, a result similar to that reported elsewhere [8,12,15]. Experiences from other centers [1,3,8,15,16] revealed that an additional 10-20% will have some sustained elevation in platelets, not to normal levels, but to levels in which excessive bleeding does not occur (partial remission), and in the remainder (10-20%), no beneficial effects will occur. Although this procedure is accompanied by low immediate postoperative mortality if the bone marrow has adequate megakaryocytes, our experience and that of other colleagues [2,5,8,9,12] with later relapse in more than one-third of the splenectomized patients, and the necessity for long-term administration of penicillin to prevent sudden and overwhelming infection, enjoin that this therapy be restricted to severely symptomatic cases who are refractory to other conventional therapeutic measures. In this series, the spontaneous remission rate of 5/15 (33%) at ≥ 3 years is about 50% of that reported from the West [5]. Therefore, our chronic cases tended to have a longer course with their disease and were probably subjected to additional complications. However, further studies with a larger number of cases are needed to verify this finding.

Infusion of intravenous gammaglobulin in children with chronic ITP is an effective, nontoxic maintenance therapy that may delay splenectomy

[17-20]. In our series, this therapy was effective in keeping the platelet count at a reasonably safe level while awaiting spontaneous remission to occur, thus avoiding or postponing splenectomy.

In conclusion, in a search for a predictor of chronic disease, some of the characteristics of our patients at presentation and their platelet count recovery after diagnosis were analyzed. The results in the cohort of cases seen initially at KKUH with ITP agree with the recent findings of Robb and Tiedeman [12] in terms of the use of platelet count at four weeks and three months following the diagnosis of ITP as a predicting factor for chronic disease. If the platelet count is $<50\text{x}10^9$/L or $<150\text{x}10^9$/L at 28 days and three months after presentation respectively, there remains a significant risk of chronic disease [12]. However, we could not find a correlation between duration of symptoms prior to presentation and outcome of disease as has been previously reported [8,12]. In addition, other factors which have been reported to be useful in predicting the course of ITP in children were not investigated in this series [13]. The most consistent finding was the increased lymphocyte proliferation in patients with chronic ITP in contrast to the acute cases.

The findings in the present study suggest that the nature of childhood ITP in Saudi Arabia is similar worldwide, but further studies, reports, and a larger series from Saudi Arabia are needed to substantiate this conclusion.

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FAT EMBOLISM SYNDROME: A CLINICAL APPRAISAL

Elamana Vijayakumar, MD, FFARCS

أجري تقييم لثماني وعشرين (٢٨) حالة من حالات متلازمة الانصمام الدهني على مدار أربع سنوات (١٩٨٧ ـ ١٩٩٠م)، وذلك فيما يتعلق بالمظاهر السريرية والدموية والكيميائية الحيوية وتحديد الإنذار. شخص الانصمام الدهني لدى مانسبته ١,٣٪ من بين ٢١١٢ مريضًا أدخلوا في وحدة العناية المركزة، وشخص أيضًا لدى مانسبته ٢,٦٪ من المرضى المصابين برضوح متعددة. حدثت متلازمة الانصمام الدهني في أعقاب الإصابة بكسور متعددة لدى ٦٠,٧٪ من الحالات. وكانت لدى ١٧,٩٪ من المرضى كسور منعزلة في عظم الفخذ. اشتملت الكسور المؤهبة الأخرى على اصابات الرأس المغلقة (٧,١٪) وبضع الشحم (٧,١٪) وإصابة الأنسجة الرخوة (٣,٦٪). حدث الانصمام بعد فترة متوسطها ٤٨ ± ٣١,١ ساعة، علمًا بأن ٦٤,٣٪ من المرضى ظهرت عليهم أعراض المتلازمة السريرية بكاملها. كان القصور التنفسي هو الأكثر تواردًا. شوهد الحبر لدى ٨٢٪ من المرضى، لكن في مناطق الإبط وتحت الترقوة في الغالب. اشتملت الأعراض الرئيسية الأخرى على الحمى (٦٧,٨٪) وفقر الدم (٦٤,٣٪) واليرقان (٥٧,١٪) ونقص الصفيحات (٤٦,٤٪) واعتلال الدماغ (٤٢,٨٪). وكان لدى ماجموعه ٦٠,٧٪ من المرضى دليل شعاعي على الإصابة بمتلازمة ضائقة التنفس الحادة. أظهر تصوير الجمجمة المقطعي بالحاسوب وذمة شاملة طفيفة لدى ١٧,٩٪ من الحالات. تلقى جميع المرضى علاجًا داعمًا، بما في ذلك التهوية الآلية لما نسبته ٧٨,٦٪، ولم يعالج أي منهم بالستيرويدات. توفي مريض واحد (٣,٨٪) خلال السنوات الأربع. نوصي بالتدبير المبكر والعناية المركزة الفعالة لأن بإمكانها تقليل الوفيات في المصابين بمتلازمة الانصمام الدهني إلى أدنى حد ممكن.

Over a four-year period (1987-1990), 28 cases of fat embolism syndrome (FES) were prospectively evaluated for clinical, hematological and biochemical manifestations and prognostication. In a total of 2,112 patients admitted to the Intensive Care Unit (ICU), 1.3% were diagnosed as having FES which was also seen in 2.6% of the patients with polytrauma. FES followed multiple fractures in 60.7% of cases; 17.9% of patients had an isolated fracture of the femur. Other predisposing fractures included closed head injury (7.1%), lipectomy (7.1%), and soft tissue injury (3.6%). The mean free interval was 48 ± 13.1 hours and 64.3% of the patients had the full clinical syndrome. Respiratory insufficiency was the most common abnormality noted. Petechiae were seen in 82% of patients but were observed mostly in the infraclavicular and axillary areas. Other principal manifestations noted included fever (67.8%), anemia (64.3%), jaundice (57.1%), thrombocytopenia (46.4%), and encephalopathy (42.8%). A total of 60.7% of the patients had radiological evidence of ARDS. Cranial computed tomographic (CT) scans in 17.9% cases showed minimal global edema. All patients had supportive management including mechanical ventilation in 78.6% and none of the patients received steroids. During the four-year period, only one patient died (3.6%). We recommend that early and aggressive critical care management can minimize mortality in patients with FES.

A profusion of publications has followed the original description of this clinical entity by Zenker in 1862. However, to date, this syndrome continues to be plagued by several diagnostic and therapeutic controversies. Although the first described syndrome occurred in a patient with a thoracoabdominal crush injury, it is widely known to follow long bone or

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From the Department of Surgery, College of Medicine, King Saud University, Abha.

Address reprint requests and correspondence to Dr. Vijayakumar: Assistant Professor, King Saud University, Abha Branch, Anesthesia, Department of Surgery, College of Medicine, P.O. Box 641, Abha, Saudi Arabia.

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pelvic fractures. The classic triad of cerebral dysfunction, pulmonary gas exchange defects, and petechial hemorrhages marks the full-blown syndrome [1]. Partial syndromes are far less commonly diagnosed, most probably due to the lack of awareness of their existence. The incidence of major trauma and associated morbidity is high in the Asir province; we attempt to define the magnitude of this life-threatening, but potentially reversible post-traumatic sequela.

Patients and Methods

All patients with fat embolism syndrome (FES) admitted to the 12-bed intensive care unit at Asir Central Hospital over a four-year period from 1987-1990 were prospectively evaluated for this study. Fat embolism syndrome (FES) was diagnosed using any two of the major criteria (respiratory insufficiency, cerebral dysfunction, and petechial hemorrhages not attributable to direct trauma) and any two of the minor criteria (fever, thrombocytopenia, lipemia, lipuria, fat globules in sputum, fundal hemorrhages on ophthalmoscopy, and hypercholesterolemia). In patients who have well established predisposing factors (e.g., long bone trauma), the development of the petechial rash (in 48-72 h) in the classical supramammary sites was considered diagnostic [2]. The patients were managed supportively with special emphasis on ventilatory support and cerebral decongestion with mannitol and controlled hyperventilation as indicated. Serial chest x-rays and blood gas measurements were performed, evaluated, and appropriate therapeutic steps undertaken, including stabilization of fractures as early as possible.

Results

A total of 28 patients (1.3%) developed clinically manifested FES among 2,112 Intensive Care Unit (ICU) admissions from 1987-1990. We had 872 polytrauma patients admitted to the ICU during these four years and the incidence of FES in the group was 2.6% (23 cases). Of the 28 patients who developed this syndrome, 24 were males (85%) with polytrauma.

The mean age of the patients was 24.7 ± 9.2 years (range 9-52 years). The mean duration of ICU stay was 7.8 ± 3.6 days, varying between 2-22 days. The mean free interval (MFI), defined as the period between the initial insult and development of the clinical syndrome, was 48 ± 13.1 h, ranging from 26-76 h. Eighteen patients (64.3%) developed the full clinical picture and the remainder had partial syndromes. Respiratory function with hypoxemia and initial hypocarbia secondary to compensatory hyperventilation was the most commonly associated clinical abnormality (89.3%). The majority of these patients (22 out of 25) subsequently developed hypercarbia necessitating active ventilatory support. Fundal hemorrhages clearly unassociated with trauma were detected in only two patients (7.1%). The incidence of the clinical, biochemical, hematological, and radiological abnormalities are summarized in Table 1.

Among the 23 patients who developed petechial hemorrhages, the distribution of the skin lesions was virtually confined to the various sites in the supramammary region (Table 2). The petechial lesions appeared on the second day, remained until the fourth day, and disappeared completely within 72

TABLE 1. *Clinical features of FES.*

Features	Patients	(%)
Clinical:		
1. Respiratory insufficiency (ARDS)	25	89.3
2. Petechial hemorrhages	23	82.1
3. Cerebral dysfunction	12	42.8
4. Fever (<38.3 °C)	19	67.8
5. Jaundice	16	57.1
6. Fundal hemorrhages	2	7.1
7. Acute renal failure	1	3.6
8. Uncompensated DIC	1	3.6
Laboratory:		
1. Anemia (HB<10g/dl)	18	64.3
2. Thrombocytopenia (<100,000/mm^3)	13	46.4
3. Fat globules in urine	8	28.6
4. Fat globules in sputum	5	17.9
5. Fat globules in blood	2	7.1
6. Hypocholesterolemia (<120mg/dl)	2	7.1
7. Uremia	1	3.6
Radiology:		
1. Chest x-ray: New infiltrates	17	60.7
2. Cranial CT (minimal diffuse edema)	5	17.9

FES = fat embolism syndrome.

TABLE 2. *Pattern of distribution of petechial hemorrhages.*

Site	Number of Patients	(%)
1. Infraclavicular	12	52.2
2. Axillary	5	21.7
3. Cervical	2	8.7
4. Facial	2	8.7
5. Conjunctival	2	8.7
6. Multiple sites	2	8.7

TABLE 3. *Associated injuries.*

Type of Injury	Patients	(%)
1. Multiple fractures	17	60.7
2. Single fractures	6	21.4
3. Isolated femur fractures	5	17.9
4. Brain injury (with fractures)	3	10.7
5. Closed head injury (without fractures)	2	7.1
6. Postoperative (Lipectomy)	2	7.1
7. Renal and fat injury	1	3.6

TABLE 4. *Respiratory supportive therapy in FES.*

Mode	Patients	(%)
1. O_2 by mask	6	21.4
2. Mechanical ventilation	22	78.6
3. Positive end-expiratory pressure	20	71.4
4. Inverse ratio ventilation (I:E = 3:1)	2	7.1
5. Tracheostomy	1	3.6

FES=fat embolism syndrome.

h after onset, regardless of the clinical state of the patients.

The clinical conditions which were associated with the development of FES are as presented in Table 3.

All the patients with bony injuries in this series developed FES prior to delayed (over 48 h) fixation of their fractures. Their definitive orthopedic management had been deferred due to hemodynamic instability or potentially life-threatening head injury. None developed recurrent FES after subsequent internal fixation of these fractures. Significantly, there were no cases of FES among polytrauma patients who had their fractures fixed within the first 24 h.

All the patients in this series needed supportive respiratory therapy (Table 4). Twenty-two patients required mechanical ventilation for a mean period of 5.7 ± 3.2 days, ranging from 2-18 days. One patient, with clinical signs of primary brainstem injury, needed a tracheostomy on the tenth day.

Only one patient in this series died. This patient had an isolated fracture of the femoral shaft and was hemodynamically stable on admission to the general orthopedic ward. During this period, the patient became confused and developed respiratory distress and petechiae on the third day (50 h) following admission and proceeded to develop severe ARDS, disseminated intravascular coagulation, acute renal shutdown, and multi-organ failure. Transfusion with 1000 ml of compatible blood produced marked unconjugated hyperbilirubinemia (41 mg/dl), which indicated significant hepatocellular dysfunction. The patient died due to unresponsive hypoxemia within 24 h of developing fulminant FES.

Discussion

It appears that Asir Central Hospital has had to cope with an average of one critically ill patient with FES approximately every two months. Of all ICU admissions in our hospital, 41.3% are attributed to polytrauma, which is a high incidence by any standard. Each day of ICU stay for a patient with adult respiratory distress syndrome (ARDS) on ventilatory support costs upwards of US$ 2,000 [3]. An average ICU requirement of nearly eight days has gross financial implications in our area. The incidence of FES of 2.89% among trauma victims compares well with the incidence of 1-5% in the published literature [4]. The higher incidence of FES in male patients (83%) in our series probably reflects the overwhelming majority of males among polytrauma victims (86.2%) which correlates with the ban on driving for women in the Kingdom.

It is important to distinguish between "fat embolism" and the clinical entity, "fat embolism syndrome" (FES). The presence of fat globules in pulmonary vasculature has been documented in 90-97% of cases after major trauma [5], as fat globules released from the ruptured adipocytes gain entry into the venous channels and embolize in the pulmonary circulation. However, a great majority of these patients are asymptomatic. While the term "fat embolism" could arguably be used for these situations, the diagnosis of "fat embolism syndrome" (FES) should be reserved for symptomatic patients only (3-5%) [6] who demonstrate at least two of the major criteria [7] (pulmonic, neurologic, or dermatologic manifestations). The exact etiology of the syndrome remains unclear and the factors influencing the susceptibility of a given patient remain undefined. Therefore, no routine clinical or laboratory parameters are able to help in predicting the development of FES [8], except the petechial rash, which has been found to be present in approximately 50% of cases [2]. This confounds any attempts at controlled trials of medications for assessing the efficacy of prophylaxis in FES.

The "mean free interval" (MFI) in our study (48 ± 13.1 h) compares well with the figures (39 ± 27 h) reported earlier and the old adage that FES develops within 48-72 h following trauma generally holds true.

We encountered a higher incidence of petechial hemorrhages (82%) compared to the expected 50%, and this may be due to the stricter exclusion criteria used in this study. Over half of the patients had the petechiae in the infraclavicular region which was twice as frequent as the axillary lesions. The extent or profusion of the lesions did not correlate with the severity of the other symptoms. None of the patients had frank convulsions and the most common central nervous system (CNS) manifestation was that of diffuse encephalopathy without localization. Anemia (64.3%) was of the normochromic normocytic type and might have been, at least in part, posthemorrhagic.

FES has been reported following non-traumatic insults such as acute pancreatitis and sickle cell disease. A subacute type of FES, often undiagnosed, has been implicated as an etiological factor in the subsequent development of multiple sclerosis [9]. While the mere presence of neutral fat globules in lung capillaries seems to produce no overt harm, dissociation of these triglyceride globules in the lung with subsequent liberation of free fatty acids (FFAs) is probably significant. These FFAs are highly irritating to the alveolocapillary membrane which leaks a protein-rich fluid into the pulmonary interstitium producing ARDS [2]. FFAs also inactivate the alveolar surfactant which contributes to further decrements in functional residual capacity (FRC) of the lungs and adds to the hypoxemia. Systemic manifestations of FES may be explained by the opening of pulmonary arteriovenous shunts which results from ARDS as well as mechanical blockade of pulmonary capillaries by fat globules. Neutral fat emboli may traverse these shunts or squeeze past the pulmonary capillaries to reach other organs, where they undergo lipolysis and release free fatty acids [4]. A patent foramen ovale, if present, may also contribute to systemic embolization. A low-grade DIC with an impaired fibrinolytic system is indicated by elevated FDPs, thrombocytopenia, and mild anemia. Intracapillary embolization with fat globules along with coagulopathy may account for the petechial hemorrhages. The reasons for the characteristic supramammary (axillary, infraclavicular, cervical, and conjunctival) distribution of the petechial hemorrhages has not yet been satisfactorily explained. Mild jaundice with elevated liver enzymes and minimal renal impairment are also commonly observed in patients with FES.

Several suggested modes of specific therapy (heparin, clofibrate, and alcohol) have fallen into disfavor, as their efficacy remains unproven. There are strong recommendations for the use of steroids both in prophylaxis [8] and therapy [11]; there are equally strong opponents to this approach as well [12]. In this series, 13 patients (46.4%) had evidence of blood in the gastric aspirate within the first 24 h following trauma and two patients were non-insulin dependent diabetics. Hence, steroids were not used in any of the patients in this study; nevertheless, the mortality in this series (3.6%) is lower than the figures previously reported in the literature [2,10]. Early and aggressive supportive therapy seems to be the rational approach, which is usually associated with a good prognosis. We are currently assessing the effects of eicosanoate blockade with a non-steroidal anti-inflammatory agent (indomethacin) in an attempt to combat the increases in bronchial blood flow which may contribute to pulmonary edema and respiratory failure [13,14]. The initial therapeutic responses are encouraging.

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PATTERN OF DEGENERATIVE ATAXIAS IN THE EASTERN PROVINCE OF SAUDI ARABIA

Adnan Awada, MD; Saad Al Rajeh, MD; Olajide Bademosi, FRCP;
Hassan Ismail, MRCP

أجريت دراسة على أنماط الرنح التنكسي على مدى ست سنوات في مستشفى الملك فهد الجامعي بمدينة الخبر في المنطقة الشرقية من المملكة العربية السعودية. وبوجود اثنتين وعشرين حالة كان تواتر المرض بين مراجعي المستشفى يعادل ٧/١٠٠,٠٠٠. كانت حالات الرنح المبكرة هي الأكثر شيوعًا، خاصة داء فريدريخ (٩/٢٢)، علاوة على أنماط أخرى غير شائعة مثل الرنح المصحوب بضعف المناسل الوظيفي والرنح مع لا أدائية في حركية المقلة. كانت هناك ست حالات من الرنح المتأخر، في حين كان الرنح (المخيخي الصرف) هو الغالب في معظم الأحيان. تمت مناقشة هذه البيانات ومقارنتها بالتقارير الأخرى، آخذين بعين الاعتبار بأن هذه الاضطرابات من النوع المتطور وأن أنماطها التصنيفية يمكن أن تتغير مع تقدم الحالة.

The patterns of degenerative ataxias as seen over a six year period at the King Fahad Hospital of the University, Al Khobar in the Eastern Province of Saudi Arabia are reported. Twenty two cases were seen, giving a hospital frequency of 7/100,000 patients. Early onset ataxias were the most common, particularly Friedreich disease (9/22). Uncommon types such as ataxia with hypogonadotropic hypogonadism and ataxia with oculomotor apraxia were encountered. There were six late onset ataxias; "pure cerebellar" ataxias were the most common. These data are discussed and compared with other reports, keeping in mind that these disorders are evolutive and their nosologic patterns can change with their progression.

Degenerative ataxias are a complex group of disorders comprising over 50 syndromes [1,2]. Their classification is difficult, despite the progress in the genetic, epidemiologic, and biochemical approaches [3]. A simple classification useful for clinicians was proposed by Harding [1] vis: (1) ataxias with known metabolic cause; (2) those with unknown cause and early age of onset; and (3) those with unknown cause and late age of onset.

The prevalence of degenerative ataxias is low: 0 to 23 per 100,000 population in different parts of the world [4-8]. Since the early report of Sjogren [9] and in other community and hospital-based studies, Friedreich ataxia (FA) remains the most common type [1,2], accounting for nearly 50% of the cases.

Statistics on the prevalence and the pattern of degenerative ataxias have not yet been defined in Saudi Arabia. In the present study, we report our experience over a six year period in the Eastern Province of Saudi Arabia.

Patients and Methods

Included in this study were all patients presenting to the Pediatric and Adult Neurology Clinics in King Fahad Hospital, the university hospital of the Eastern Province of Saudi Arabia between January 1985 and December 1990 with a progressive cerebellar ataxia with or without a family history and not related to a malformation or tumor. Cases with cerebellar ataxia in association with malignancy, alcoholism, anticonvulsant therapy, or hypothyroidism were excluded.

All patients underwent a complete neurological examination on admission to the clinic. Their personal and familial histories were recorded. Special attention was paid to the presence of skeletal

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From the Department of Neurology (Drs. Awada, Bademosi, Ismail), College of Medicine and Medical Sciences, King Faisal University, Dammam, and Division of Neurology, Department of Internal Medicine (Dr. Al-Rajeh), King Saud University, Riyadh.

Address reprint requests and correspondence to Dr. Awada: Senior Staff Neurologist King Fahad National Guard Hospital, P.O. Box 22490, Riyadh, 11426, Saudi Arabia.

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deformities such as pes cavus or scoliosis. All the patients had been investigated for blood cell count, electrolytes, glucose, blood urea nitrogen, creatinine, cholesterol, and hepatic function tests. Electrocardiogram, brain computerized tomographic (CT) scan, and motor nerve conduction study with electromyogram were also performed in all cases. The following investigations were performed in some patients: sensory nerve conduction studies, serum levels of folic acid, vitamin B_{12}, vitamin E, cerebrospinal fluid (CSF) study including protein electrophoresis, visual, auditory and somatosensory evoked potentials, and magnetic resonance imaging (MRI). Other investigations were also performed when clinically indicated (e.g., hormonal assays, immunity profile, chromosomal study, etc.).

Results

The diagnosis of degenerative ataxia was initially established in 27 cases. Five cases were subsequently eliminated from this study: 1) two cases (brother and sister) with a brain biopsy proved a childhood form of ceroid lipofuscinosis in which ataxia was a marginal sign while the clinical picture was dominated by dementia, visual loss, and seizures; 2) three sisters with ataxia, pes cavus and signs of sensorimotor demyelinating neuropathy where the final diagnosis was the so called "Roussy-Levy Syndrome" which most authors now admit to be a special form of the hereditary sensorimotor neuropathy type I [10-12].

The remaining 22 patients (14 males and 8 females) constituted approximately 1% of the neurology patients. Their hospital frequency was 7/100,000 patients. Nineteen patients (12 males and 7 females) were Saudi nationals and three were expatriates (a Syrian female, a Yemeni male and a Sudanese male).

The age of onset ranged from 3 to 47 years (mean age 13.6 years). In ten cases, the disease started prior to age ten. The onset was during the second decade in another six cases, and in the fourth and fifth decade in the last six cases. There were similar cases in the family in eight cases (36%). Table 1 shows the relative frequencies of our cases in comparison with that reported in other regions (8,13).

Ataxias With Early Age of Onset

The disorder was considered to be of early onset (EO) when the first symptoms and signs appeared prior to age 20. Friedreich ataxia was the most

TABLE 1. *Patterns of inherited ataxias reported from Saudi Arabia, Libya [8], and United Kingdom [13].*

	Present Study (N=22)	Sridharan(Libya) (N=28)	Harding (UK) (N=157)
EARLY ONSET ATAXIA	16 (72%)	17 (61%)	145* (92%)
Friedreich disease	9 (41%)	3 (11%)	106 (67.5%)
w/ retained reflexes	2 (9%)	13 (46%)	22 (14%)
Ataxia telegiectasia	-	1 (1.5%)	4 (2.5%)
w/ optic atrophy	1 (5%)	-	1 (0.64%)
w/ hypogonadism	2 (9%)	-	-
w/ oculomotor apraxia	2 (9%)	-	-
LATE ONSET ATAXIAS	6 (27%)	11 (39%)	12 (8%)
pure cerebellar	3 (13%)	3 (11%)	1 (0.64%)
w/ optic atrophy/ opthalmoplegia/ extrapyr. sc	2 (9%)	2 (7%)	9 (5.8%)
w/ albinism	1 (5%)	-	-
w/ retinal pigmentary degeneration	-	6 (21%)	1 (0.64%)

* Other early onset ataxias in Harding's series include: associated mental retardation, retinitis pigmentosa, congenital deafness, x-linked transmission with essential tremor and myoclonus (around 1% each).

frequent entity (9 cases). The classical features of this disease were present in our patients with the following frequency: first symptoms between 5 and 20 years of age, cerebellar ataxia in 9 cases, dysarthria 9, decreased or absent tendon reflexes 9, pes cavus 8, decreased vibration sense 7, Babinski sign 6, and scoliosis in 5 cases. Brain computerized tomography (CT) scan revealed cerebellar atrophy dominant on the vermis in 6/9 cases confirmed by magnetic resonance imaging in one case. Usual blood investigations were normal in eight patients and revealed diabetes mellitus in one case only. Serum folate, vitamin B_{12} and vitamin E levels were normal in all the cases where they were measured. Cerebrospinal fluid (CSF) studies were normal in the nine cases. Nerve conduction studies revealed mild decreased motor conduction velocity of the peroneal nerve (40 and 42 m/sec) in 2/9 patients. Sensory potential of the sural nerve was not recorded in two patients of four where this procedure was performed.

Seven patients presented with other types of ataxia at early onset. The final diagnosis was ataxia with retained reflexes in two, ataxia with hypogonadism in two, ataxia with oculomotor apraxia in two, and Behr disease in the remaining patient. The patients' clinical features and results of the main investigations are reported in Table 2.

The two patients with ataxia and hypogonadism (Cases 3 and 4) were brothers born from first degree cousins. They were examined at age 20 and 17, respectively. The signs of hypogonadism consisted of small testicles and sparse pubic and axillary hair. The older brother was more severely affected. The following serum hormonal assays were performed and all showed reduced values in both patients: FSH: 0.8 and 1m iu/ml, respectively (normal 1.5 - 18 m iu/ml); LH: 0.5 and 1.2m iu/ml (normal 3 - 22) and testosterone 5.8 and 20.3 ng/ml (normal 300 - 1000). Cortisol, TSH, T3 and T4 had normal levels. LH-RH test did not provoke any increment in LH and FSH levels. At age 23, the older brother became bedridden and severely dysarthric.

There was no cutaneous or conjunctival telangiectasis in the two cases (Nos. 5 and 6) with ataxia and oculomotor apraxia. Brain MRI was normal in Case 6, and in both CSF studies, protein electrophoresis, immunoglobulin A,G,M and E levels, and alpha fetoprotein levels were normal.

Ataxias of Late Age Onset

Late onset (LO) cerebellar ataxias were diagnosed in four unrelated patients and two related cases (father and son). The age of onset of the first symptoms was between 35 and 47 years. In three cases, including two from the same family, pure cerebellar degeneration was diagnosed. Two others had associated akinesia and rigidity suggesting olivopontocerebellar degeneration. A Syrian female had associated total albinism, decreased visual acuity since childhood, and pendular nystagmus. She had a sister with the same symptoms who was not examined as she was living in Syria. None of these patients had signs of autonomic failure. The appropriate investigations (brain CT, MRI, CSF

Table 2. *Ataxias of early age of onset (except Friedreich disease).*

Case	Age of Onset	Sex	Cerebellar	Pyramidal Signs	DTR	Pes Cavus	Other Features	Cerebellar CT
1	13	M	+	+	N	+	-	Atrophy
2	14	F	+	+	N	-	-	N
3	12	M	+	+		+	MR, Hypogonadism	Atrophy
4	12	M	+	+	↗	+	MR, Hypogonadism	Atrophy
5	4	M	+	-	↘	-	Athetosis, oculomotor apraxia	N
6	3	F	+	-	↘	-	Athetosis, oculomotor apraxia	N
7	3	M	+	+	↗	-	Optic atrophy	Atrophy

DTR=deep tendon reflexes; MR=mental retardation.

studies, evoked potentials, appropriate blood tests) excluded multiple sclerosis and secondary cerebellar degeneration.

Comments

Prevalence of degenerative ataxias varies in different regions of the world. The prevalence rate for 100,000 population has been found to be zero in Rochester, New York USA, 0.3 in Scotland, 1 in Iceland, 2 in Sweden, 7 in England, and 13-23 in Norway [4]. The sparse information from developing countries suggests that these diseases are extremely rare in Black Africa [6,7] and seem relatively frequent in Libya with an estimated point prevalence of 4.8 per 100,000 population [8] and in Tunisia from where 392 cases belonging to 188 families were recently reported [14]. In a recent survey of neurological disorders in a community of more than 22,000 inhabitants in the Eastern Province of Saudi Arabia [15], no cases of inherited ataxias were encountered. The calculated hospital frequency from our cases was 7/100,000. The true prevalence rate in our region is probably between these two figures.

Patterns of inherited ataxias are also variable. Friedreich disease is the most common entity in almost all the Western countries [9,10,16] and constituted 58% of the cases reported by Ben Hamida et al [14] in Tunisia. Sridharan et al [8] found that it is relatively rare in Libya where the most common form was the EO cerebellar ataxia with retained reflexes. In India, FA is thought to be less common than an indigenous form associating ataxia of late onset with choreic movements and slow eye movements [17].

Our results suggest that patterns of inherited ataxias encountered in Saudi Arabia are not very different from those reported from Western countries (Table 1) or Tunisia [14]. FA was seen in 9/22 of our cases and ataxias of late onset in 6/22. The features of FA in our patients were similar to those reported by Harding [18]. However, some varieties of ataxia were found with a relatively high frequency in our series. No case of ataxia with hypogonadism or ataxia with oculomotor apraxia was reported in a large series conducted by Harding [13] while two cases of each of these types were found in ours. Ataxia with hypogonadism has been rarely reported [19,20] and both associated hyper and hypogonadism have been described. Moreover, some authors [19] have pointed to a hypothalamic primary deficiency while others [20] to a pituitary one. Our cases suggested a hypogonadotropic hypogonadism due to a pituitary deficiency as there was no response to the LH-RH test.

Ataxic oculomotor apraxia is a syndrome which has been individualized recently [21]. It seems to have a close relationship to ataxia-telangiectasia and, in some families, both conditions have been described [22]. In addition, ataxic oculomotor apraxia has been previously described in Saudi Arabia [22] and in Yemen [21]. Our two patients presented with a typical picture, but they were four and six years of age, respectively and it is known telangiectasia can be absent at these ages and appear later on.

The "pure cerebellar" ataxia was the most common form of late onset ataxia in our cases. This was different from that which was reported from Libya [8], the United Kingdom [13], and India [16]. However, late onset ataxias are evolutive diseases and many cases can be "pure cerebellar" at their first stages and non-cerebellar symptoms and signs can appear later on [23].

In conclusion, several forms of degenerative ataxias exist in the Eastern Province of Saudi Arabia and their overall prevalence is probably in the same range as those reported from other places. Early onset ataxias, and more particularly FA, are the most common ones. Some unusual nosologic types have been encountered, but these diseases are evolutive and their evolution can be towards more common types.

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BILHARZIAL AND NONBILHARZIAL BLADDER CANCER IN ASIR: A COMPARATIVE CLINICOPATHOLOGICAL STUDY

Sugandh D. Shetty, FRCS(Ed); Ahmed I.A. Ibrahim, FRCS(Ed);
Krishna P. Patil, MCh Urology, FRCS (Ed); Nadir A. Morad, FCAP;
Nagalingam Anandan, FRCS(Ed); Praful Khurana, MD

تم تصنيف ثمانية وأربعين مريضًا بسرطان المثانة من بين ست وتسعين حالة متتالية من السرطان البولي التناسلي، إلى مجموعتين بلهاريسية وغير بلهاريسية تبعا للفحص النسيجي وذلك لتقصي أثر داء البلهارسيا في سلوك الورم. وبالرغم من توطن البلهارسيا في المنطقة، إلا أن ٤٨/١٠ (٢١٪) من مرضانا عانوا من السرطان البلهاريسي، ومن هؤلاء كان ثمانية مرضى (٨٠٪) مصابين بسرطانة حرشفية الخلايا، بينما أصيب اثنان منهم (٢٠٪) بسرطانة غدية. من بين المرضى الثمانية والثلاثين المصابين بالسرطان غير البلهاريسي، أصيب خمسة وثلاثون منهم (٩٢٪) بسرطانة الخلايا الانتقالية، بينما أصيب ثلاثة منهم (٨٪) بسرطانة حرشفية الخلايا. حدثت الإصابة بالسرطان البلهاريسي لدى الذكور في وقت أبكر من السرطان غير البلهاريسي ($P < 0.05$) كانت الأورام مستفحلة جدًا (T3 and T4) إبان المراجعة الأولى لدى المرضى العشرة الذين يعانون من السرطان البلهاريسي بالمقارنة مع ٣٨/٢٢ (٥٨٪) من المرضى الذين يعانون من السرطان غير البلهاريسي ($P<0.05$) . لم نجد فروقًا هامة عند مقارنة الملامح السريرية والمخبرية في المجموعتين. نستنتج أن سرطان الخلايا الانتقالية في منطقة عسير هو أكثر أنواع سرطان المثانة تواردًا. غير أن سرطان المثانة المصاحب لداء البلهارسيا يكون في الغالب من النوع الحرشفي ويحدث في سن مبكرة، ويكون في مرحلة متقدمة حين المراجعة الأولى.

A total of 48 bladder cancer patients out of 96 consecutive genitourinary cancer cases were divided into bilharzial and nonbilharzial groups on a histological basis in order to investigate the impact of bilharziasis on tumor behavior. Despite being a bilharzial endemic area, only 10/48 (21%) of our patients had bilharzial cancer (BC) of whom 8 (80%) had squamous cell carcinoma (SCC) and 2 (20%) had adenocarcinoma. Out of 38 patients with nonbilharzial cancer (NBC), 35 (92%) had transitional cell carcinoma (TCC), and 3 (8%) had SCC. BC in males presented at a younger age than NBC ($P<0.05$). All ten patients with BC presented with deeply invasive (T3 and T4) tumors as compared to 22/38 (58%) with NBC ($P<0.05$). Comparison of clinical and laboratory features in both groups did not reveal any significant difference. We conclude that in the Asir region, TCC is the most common bladder cancer. However, with bilharziasis, bladder cancer tends to be of the squamous type and presents at an earlier age and at an advanced stage.

The association between urinary bilharziasis and bladder cancer is well documented [1-5]. The high incidence of bladder cancer with urinary bilharziasis in Egypt contrasts with the lower figures from other bilharzial endemic areas such as Sudan, Zambia, and Iraq [4-7]. Saudi Arabia is a vast country where the prevalence of urinary bilharziasis varies from one region to another [8,9]. A previous study indicated that among 254 bladder biopsies carried out at this center, 35% were associated with bilharziasis. Scarcity of studies comparing bilharzial to nonbilharzial bladder cancer from regions such as ours prompted us to look into the impact of bilharziasis on the behavior of bladder cancer. We report our experience in this communication.

From the Department of Urology (Drs. Shetty and Ibrahim), and Department of Pathology (Dr. Morad), College of Medicine, King Saud University, Abha, and Department of Urology (Drs. Patil and Anandan), Asir Central Hospital, Abha.

Address reprint requests and correspondence to Dr. Ibrahim: P.O. Box 1544, Abha, Saudi Arabia.

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Material and Methods

Asir Central Hospital in Abha is a referral hospital for the Asir Province of Saudi Arabia and receives most of the cancer patients of the region. Out of a total of 96 consecutive genitourinary cancer cases seen during the past five years, 48 were bladder cancers. The patients' age, sex, history of bilharziasis, living habitat, clinical and important laboratory features were noted. The radiological evaluation was performed using intravenous urography, ultrasonography and computed tomography (CT) scan. Staging was carried out by examination under anesthesia and histology of cystoscopic bladder biopsy and cystectomy specimens. TNM staging was used and tumor grading was carried out according to the World Health Organization (WHO) classification [10,11]. Patients were divided into bilharzial and nonbilharzial groups according to the histological finding of ova of schistosoma hematobia within the tumor or in the adjacent bladder biopsy. Tumor type, tumor stage, and age at presentation were compared in both groups in addition to clinical and laboratory features. Statistical significance of the differences was assessed by Student's t-test and Fisher's exact test [12]. Five percent was used as the level of significance.

Results

A total of 48 (50%) out of 96 genitourinary malignancies were bladder cancer. Ninety-five percent of the patients were Saudi nationals.

Overall, there were 40 males and eight females (M:F = 5:1) and in BC the M:F ratio was 2.3:1. The mean age for males with NBC was 62.36±14.13 (n=33) years compared to 50±7.59 (n=7) years in BC ($P<0.05$) (Figure 1).

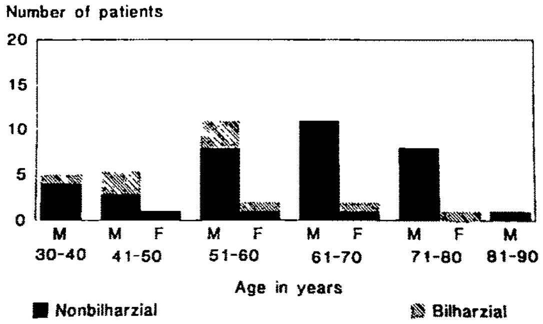

FIGURE 1. Age and sex distribution in bladder cancer.

TABLE 2. *Histological type and tumor stage in relation to bilharziasis.*

Tumor Size	Tumor Stage		Histological Types			
			TCC	SCC	ADC	Total
Bilharzial	T1	T2	0	0	0	0
Bladder cancer	T3	T4	0	8	2	10
Non-bilharzial	T1	T2	16	0	0	16
Bladder cancer	T3	T4	19	3	0	22
Total			35	11	2	48

TCC=transitional cell carcinoma; SCC=squamous cell carcinoma; ADC=adenocarcinoma.

Clinical features such as hematuria and palpable suprapubic mass were similar in both groups. The hemoglobin was identical in both groups. Although none of the BC presented with uremia, 6/38 (16%) of NBC had serum creatinine of more than 200 umol/L (Table 1).

Out of 38 patients with NBC, 35 (92%) had TCC whereas 8/10 (80%) of BC had SCC. None of the BC patients had TCC. The difference between histological types in the two groups was significant ($P<0.05$). All patients with BC were deeply invasive (T3 and T4) compared to 22/38 (58%) of NBC ($P<0.05$) (Table 2).

Discussion

In a series of 7,251 cancer cases seen at a referral center in Riyadh, Saudi Arabia, it was noted that bladder cancer had a crude relative frequency of only

TABLE 1. *Clinical and laboratory features.*

Features	NBC No.	NBC (%)	BC No.	BC (%)	*P* value
Hematuria	32	84	7	70	$P > 0.05$
Palpable mass	10	26	5	50	$P > 0.05$
Hemoglobin (gm/dl) (mean ± SD)	11.75 ± 2.55		11.9 ± 2.01		$P > 0.05$
Uremia 200 umol/L (creat >)	6	16	0		$P = 0.22$

NBC=nonbilharzial bladder cancer; BC=bilharzial cancer.

3.7% and that of the Southwestern region was 6% which was attributed to the high prevalence of bilharzial infestation [13]. A recent study from this region confirms that bladder cancer is the fourth most common cancer found in males and has a relative frequency of 9.4% among other cancers [14]. Urinary bilharziasis is indeed endemic in the southern region of Saudi Arabia and the prevalence varies from 1.7-7.6% [8,9]. In our study, only 21% of bladder cancers were bilharzial and 79% were non-bilharzial. Sixty-seven percent of the former came from the endemic lowlands of Tihama plains with an agrarian lifestyle. BC is not a common problem of the highland where the water supply comes from the desalination plant and deep wells as opposed to the lowland bilharzial areas where water ponds prevail. The 21% BC rate is in keeping with studies from Iraq and Zambia where it varies from 17-32% [4,5,7] and is nowhere near the 75-84% from Egypt [1,15]. In our study, 13/48 patients were inhabitants of the endemic bilharzial area of lowlands. Six (46%) had BC which remains lower than that from Egypt due perhaps to the sparse farming in the Tihama lowlands compared to Egypt. Al-Shukri et al [16] also reported a 75% BC rate from Kuwait where most of the patients were foreign workers originating from high bilharzial endemic areas.

The relatively younger age of our male patients with bilharzial cancer is in agreement with reports from other endemic areas [2,5,17]. The comparison was not valid in females due to the small number. The overall male to female ratio of bladder cancer in our study is similar to the ratio of 4:1 reported from the United Kingdom (UK) and USA [18,19]. However, the male to female ratio in our bilharzial patients is not similar to 5:1 or greater as reported from other bilharzial endemic areas [2]. This may be because the number of patients is small and females are also actively involved in farming in our endemic areas.

Since comparison of clinical and laboratory features did not reveal any significant differences, histology seems to be the mainstay of differentiating bilharzial and nonbilharzial bladder cancers. Of all our bladder cancers, 73% were TCC, 23% SCC, and 4% adenocarcinoma, contrasting with those from Iraq where SCC and TCC formed 46% and 43%, respectively. However, similar to our study, 72% of BC in Iraq was SCC [4]. A high incidence of SCC was also reported from Zambia (71%) and Egypt where SCC forms 68% of bilharzial and 50% of nonbilharzial cancers [2,5,15]. We had no patients with TCC in the bilharzial group contrasting with 16-25% TCC reported from other endemic areas [2,4,5]. However, in view of our hospital-based study with relatively fewer number of cases, comparison may not be adequately valid.

Two-thirds of our bladder cancer patients had advanced disease at presentation which compares well with other studies [2,7,20,21]. All the ten patients with BC were advanced T3 and T4 tumors as compared to 58% of NBC. Seventy percent of our advanced BCs were low grade tumors as compared to 41% of stage-matched NBC, a difference which again does not reach statistical significance. This contradicts with the well known fact that bilharzial cancers tend to be low grade [15,21]. Our findings probably are again due to a small sample size, although no previous study has made any comparison of the grade in stage-matched bilharzial and nonbilharzial cancers.

In conclusion, despite being an endemic bilharzial zone, TCC was the most common bladder cancer found in this region of Saudi Arabia. Bilharziasis was present in 21% of bladder cancers which were predominantly SCC (80%) presenting at an earlier age and at an advanced stage. However, there were no differences noted between the clinical and laboratory features in the two groups.

Acknowledgment

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THE STANDARD PHYSICAL GROWTH CHART FOR SAUDI ARABIAN PRESCHOOL CHILDREN

Abdulrahman S. Al-Frayh, MD, Fachartz; Elijah A. Bamgboye, PhD(Lond);
Mohammed A. A. Moussa, PhD(Edin)

تعرض هذه الدراسة رسومًا بيانية لنمو الأطفال في مرحلة ما قبل المدرسة استنادًا إلى بيانات شرائحية عن السكان في مدينة الرياض في المملكة العربية السعودية. تم تصميم الرسوم البيانية للوزن والطول حسب العمر بصورة منفصلة لكل من الصبيان والبنات. كان وزن الصبيان يفوق وزن البنات في كل الأعمار ضمن هذه الفئة. كان الصبيان أيضًا أطول من البنات بعد السنة الأولى من العمر. ونظرًا لأن القصور في نمو الأطفال في المملكة العربية السعودية بالمقارنة مع المقاييس المعتمدة دوليًا للسكان قد يعزى إلى عوامل وراثية وبيئية، فإن الرسوم البيانية المقدمة تكفي لتكون مقياسا لمراقبة نمو الأطفال السعوديين بشكل خاص ونمو الأطفال في منطقة الخليج بشكل عام.

This study presents growth charts of preschool children based on cross-sectional data of the population in Riyadh, Saudi Arabia. Charts on weights and heights per age were designed separately for boys and girls. Boys consistently weighed more than girls for this age group at every age. Also, the boys were taller than the girls after the age of one year. Since the growth deficits in children from Saudi Arabia compared with internationally recommended reference populations may be attributed to genetic and environmental factors, the charts presented will suffice as a standard in monitoring the growth of Saudi children in particular and those in the Gulf Region in general.

There is a dearth of information on the growth patterns of Saudi preschool children [1,2]. Previous reports have been based on sample sizes too small to minimize sampling errors in the estimates [2-5]. In a comparison of the physical growth of Saudi children from birth to age five years according to the internationally recognized reference populations, statistically significant growth deficits have been observed [3,6]. The consensus has been to attribute these growth deficits to genetic and environmental factors rather than infection and malnutrition [3,6].

Thus, it is essential to develop a standard growth chart for use in the Kingdom of Saudi Arabia and in the Arabian Gulf region [6,7]. The present analysis shows the growth chart which was calculated using the cross-sectional data from the Riyadh population for preschool children selected randomly from the different socioeconomic classes.

Material and Methods

Population and Sample

The methodology of the cross-sectional survey of preschool children carried out in the city of Riyadh and on which the present analysis was based has been previously described in the literature [6,8]. However, the most important elements are highlighted. The final sample of children was obtained from a three-stage stratified cluster sampling procedure. The 93 administrative areas in Riyadh were initially divided into six socioeconomic homogenous strata based on the socioeconomic interpretation of the Central Department of Statistics, Ministry of Finance and National Economy, Saudi Arabia. A total of 17 areas was selected by simple random method during the first stage of sampling. During the second stage, a simple random sample of

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From the Department of Pediatrics (Dr. Al-Frayh), and the Department of Family and Community Medicine (Drs. Bamgboye and Moussa), King Saud University, College of Medicine, Riyadh.

Address reprint requests and correspondence to Dr. Al- Frayh: King Saud University, Department of Pediatrics (39), College of Medicine, P.O. Box 2925, Riyadh 11461, Saudi Arabia.

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224 roads was selected from a total of 1,376 roads in the selected 17 areas. Finally, during the third stage, a random sample of blocks in which houses on selected roads had been subdivided was selected and all preschool children in one of every two houses were included in the study [8].

Data Collection

The data were collected by personal interviews and anthropometric measurements. There were five interviewing teams and each team included a field supervisor, anthropometrist, and a pediatrician who was responsible for the clinical examination of all preschool children. Any child diagnosed as clinically unsuitable by the pediatrician on the evidence of any illness such as chronic disease or malnutrition was excluded from the study. The mothers of the selected children were interviewed by trained interviewers while the nurse anthropometrists recorded the measurements of infants and children. All anthropometric measurements which were recorded utilized procedures recommended by Jelliffe [9]. Standing height was measured using a stadiometer (Harpenden) and weight was measured using a balance beam (Seca). For children younger than two years of age, the Harpenden measuring board was used to measure supine length and weight was measured using a baby scale.

Statistical Analysis

The data were processed on the IBM mainframe of the King Saud University Computer Center using the BMDP software computer package. Growth charts were effected through fitting the least squares polynomial regression model of degree three, using age as an independent variable and the percentiles as the dependent variable [10]. This cubic polynomial regression provided a better fit to our data than the spline polynomial regression method [11]. The graphics facility in the statistical analysis system (SAS/GRAPH) software package was used to plot the growth curves [12]. A comparison of the nutritional indicators with the reference population recommended by the World Health Organization (WHO) has been previously reported [5,6]. However, the standard scores distribution of weight/height/age for males and females separately expressed multiples of the standard deviation (SD) of the reference population were analyzed using the WHO "Anthro" software program [13].

Results

Complete data from a total of 3,795 children, 55.2% males and 44.8% females, aged 0-5 years on basic anthropometric measurements of age, weight, and height were collected. The minimum number of children in each age category was 279, a number far in excess of the recommended minimum number of 250 children by Waterlow et al [14]. The distribution of weight for height of the children at each age expressed in multiples of the standard deviation of the NCHS median are presented in Tables 1 and 2 for both sexes. The distribution is positively skewed with nearly 20% of the male and female children below 2.0 SD of the reference population median. On the average, the proportion of children below this critical cut off Z score, usually interpreted as an indicator of wasting, significantly decreases with increase in age. This decrease is, however, more pronounced in females than in males. When high weight for height was considered at each age, the proportion was significantly higher in females than in males, and a higher proportion of males (65%) than

TABLE 1. *Percentage of weight for height of Saudi Arabian male children aged 0-5 years in multiples of SD scores of the NCHS/CDC reference population in each age group.*

Age in months	No. of children (1992*)	SD scores of weight for height (% of Age-group)				
		≤ - 2 SD	-1.99 SD to - 1 SD	-0.99 SD to 1 SD	1.1 SD to 1.99 SD	≥2 SD
< 6	224	33 (14.7)	44 (19.6)	112 (50.0)	23 (10.3)	12 (5.4)
6-11.99	229	54 (23.6)	59 (25.8)	91 (39.7)	11 (4.8)	14 (6.1)
<12	453	87 (19.2)	103 (22.7)	203 (44.8)	34 (7.5)	26 (5.7)
12	341	103 (30.2)	105 (30.8)	113 (33.1)	13 (3.8)	6 (1.8)
24	300	52 (17.3)	116 (38.7)	122 (40.7)	9 (3.0)	1 (0.3)
36	297	68 (22.9)	88 (29.6)	116 (39.0)	18 (6.1)	4 (1.3)
48	263	49 (19.6)	72 (27.4)	118 (44.9)	17 (6.5)	5 (1.9)
60	268	41 (15.3)	86 (32.1)	123 (45.9)	13 (4.9)	5 (1.9)
All ages	1922	400 (21.1)	570 (29.7)	795 (41.3)	104 (5.4)	47(2.4)

* Children with Z-score values outside the range - 4 and + 6 were excluded from the analysis; SD=standard deviation.

TABLE 2. *Percentage of weight for height of Saudi Arabian female children aged 0-5 years in multiples of SD scores of the NCHS/ CDC reference population in each age group.*

Age in months	No. of children (1525*)	SD scores of weight for height (% of Age-group)				
		≤ - 2 SD	-1.99 SD to - 1 SD	-0.99 SD to 1 SD	1.1 SD to 1.99 SD	≥2 SD
< 6	157	25 (15.9)	36 (22.9)	76 (48.4)	15 (9.6)	5(3.2)
6-11.99	194	50 (25.8)	50 (25.8)	73 (37.6)	14 (7.2)	7(3.6)
<12	351	75 (21.4)	86 (24.5)	149 (42.4)	29 (8.3)	12(3.4)
12	300	61 (20.3)	76 (25.3)	130 (43.3)	19 (6.3)	14(4.7)
24	234	40 (17.1)	66 (28.2)	116 (49.6)	6 (2.6)	6(2.6)
36	226	45 (19.9)	71 (31.4)	90 (39.8)	15 (6.6)	5(2.2)
48	218	25 (11.5)	58 (26.6)	113 (51.8)	14 (6.4)	8(3.7)
60	246	45 (18.3)	69 (28.0)	105 (42.7)	17 (6.9)	10(4.1)
All ages	1575	291 (18.5)	426 (27.0)	703 (44.6)	100 (6.3)	55(3.5)

* Children with Z-score values outside the range - 4 and + 6 were excluded from the analysis; SD=standard deviation.

TABLE 3. *The mean height and standard deviation of Saudi Arabian children aged 0-5 years by age/sex.*

Age in mos.	Male No. of children	Male Mean±SD	Female No.of children	Female Mean ±SD
0	279	62.1 ± 13.6	189	62.5 ± 13.4
6	266	70.6 ± 10.1	222	72.7 ± 15.5
12	365	77.5 ± 7.7	328	77.7 ± 10.3
24	320	87.8 ± 9.2	242	85.9 ± 7.8
36	308	95.4 ± 8.4	236	93.7 ± 10.2
48	275	100.5 ± 10.2	227	99.0 ± 10.8
60	282	1071 ± 9.1	256	106.3 ± 8.5

SD = standard deviation.

TABLE 4. *The mean height and standard deviation of Saudi Arabian children aged 0-5 years by age/sex.*

Age in mos.	Male No. of children	Male Mean ±SD	Female No. of children	Female Mean ±SD
0	279	5.3 ± 1.5	189	5.1 ± 1.4
6	266	7.7 ± 1.4	222	7.5 ± 4.4
12	365	9.5 ± 1.5	328	9.3 ± 1.9
24	320	11.6 ± 2.0	242	11.4 ± 2.0
36	308	13.3 ± 2.9	236	13.2 ± 2.5
48	225	15.0 ± 2.9	227	14.8 ± 3.1
60	282	16.7 ± 2.8	256	16.4 ± 3.2

SD = standard deviation.

females (60%) were within the (-1.0 SD and 1.0 SD) normal range of the reference population. The mean and standard deviation of the heights and weights of the children are presented in Tables 3 and 4. The girls appear slightly taller than the boys during the first year of life, but soon after, the situation reversed. The weight patterns of boys and girls appeared similar at each age, even though the boys seemed to have higher weights. The five percentile points (5th, 25th, 50th, 75th, and 95th) of weight and height for age that were plotted separately for boys and girls are shown in Figures 1(A and B), and 2 (A and B),

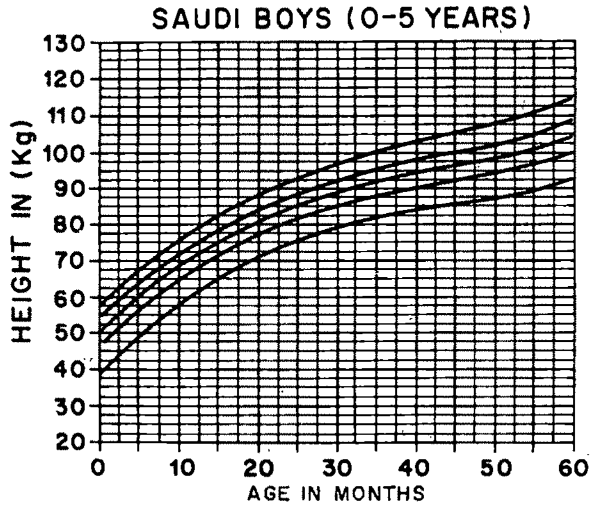

FIGURE 1a: Stature by age: Boys, 0-60 months

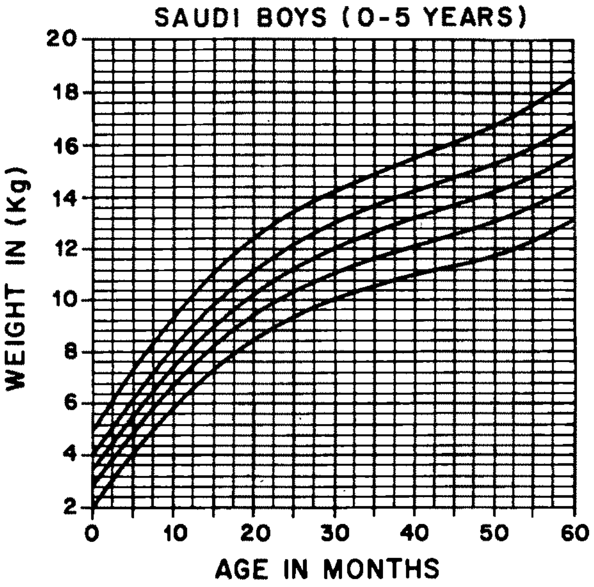

FIGURE lb: Weight by age: Boys, 0-60 months

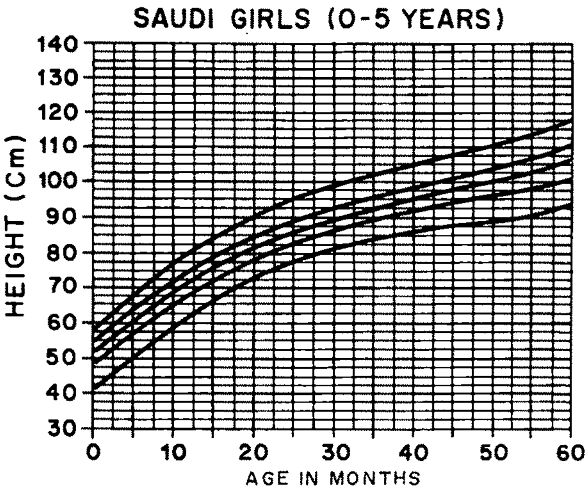

FIGURE 2a: Stature by age: Girls, 0-60 months

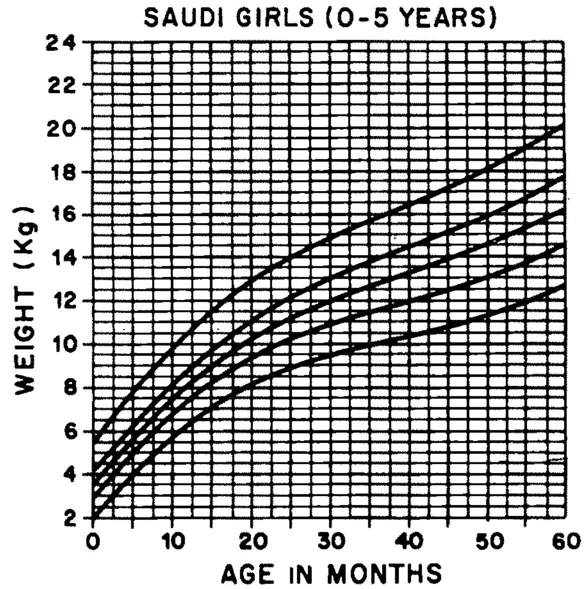

FIGURE 2b: Weight by age: Girls, 0-60 months

Discussion

The recommendation of the World Health Organization (WHO) to use the United States NCHS/CDC anthropometric data as a reference population in the analysis and interpretation of anthropometric data was used to facilitate intercountry comparisons. In addition, the data base in many countries remains poor in quality and quantity and was therefore considered to be unreliable [13,14]. The present anthropometric data on preschool children, although collected in a cross-sectional study, a practical study design found widely acceptable to statisticians, is of high quality and quantity [13,15,16]. The design of the study is reproducible and the sample of children in each age and sex group is higher than the number recommended by WHO [13]. In addition, the anthropometric measurements were recorded carefully by well trained and experienced professionals using standard and reliable equipment [8].

The high proportion of preschool Saudi children below the 2.0 SD of the NCHS/CDC reference population median of weight for height observed in this study can be explained in terms of the different population characteristics of Saudi Arabia compared to the standard used in the American population. Previous studies have shown differences in growth patterns between populations [5,7,18]. The implications of the deficits in the growth patterns of preschool children compared to the reference population have been previously discussed. The studies highlight a genetic control versus nutritional deficiencies [2,5,6,19].

Conclusion

The general pattern of growth observed in this study, whereby boys consistently had higher weights than girls at every age, is similar to that which has been previously reported for other countries [17,18,20-22]. It is also well documented that the birth weight of boys is higher than that of girls and with good nutrition and environmental sanitation, is expected to continue until, perhaps, the age of puberty for girls [19,23]. However, the growth patterns observed are comparable to situations found in similar communities in the Middle East [20,21-26]. Although the present study is based on the population in Riyadh, Saudi Arabia, the selection of sample covered all socioeconomic classes of Saudi Arabia [8]. While a prospective anthropometric study of children from birth to required age is desirable [19], the present growth charts may serve as a more reliable standard growth chart to monitor the growth of preschool Saudi children in particular and Gulf states in general.

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CI-990 (PD 131112): A NEW QUINOLONE PRODRUG

S.M. Hussain Qadri, PhD, FRCPath, FAAM. Diplomate ABMM; Yoshio Ueno, RT;
Hishama Saldin, BSc, AASM; John Markley Burdette, MT, (ASCP); Gordon C. Lee, FIMLS

تم في المختبر تحديد استعداد ١٠٢١ ذرية من المعزولات السريرية الحديثة للتأثر بالفلوروكوينولون الجديد (CI-990) (PD 131112) ومقارنتها بـ (CI-960) ، سيبروفلوكساسين، فليروكساسين، لوميفلوكساسين، نورفلوكساسين، بيفلوكساسين، سبارفلوكساسين، تيمافلوكساسين. كان معدل التركيز التثبيطي الأدنى من CI-990 المطلوب لأكثر من ٩٠٪ من المعزولات ٠,٠٣ ـ ٠,٥ لأفراد زمرة الأمعائيات و ٠,١٢ ـ ٢,٠ للزائفة الزنجارية و ٠,٠٣ ـ ١,٠ لـ *Aeromonas Hydrophila* و ١,٠ ـ ٢,٠ لـ *Acinetobacter Calcoaceticus* و ٠,٥ ـ ٢,٠ للبروسيلة المالطية و ٠,٠٦ ـ ١,٠ للعنقوديات و ١,٠ ـ ٢,٠ لمكورات المعوية. وتعادلت فعاليتها المضادة للجراثيم مع أنواع الفلوروكينولون الأخرى أو تفوقت عليها حين تم اختبارها ضد معظم الجراثيم سلبية الغرام وإيجابية الغرام بما في ذلك المكورات المعوية.

In vitro susceptibility of 1021 strains of recent clinical isolates was determined against the new fluoroquionolone CI-990 (PD 131112) and compared with CI-960, ciprofloxacin, fleroxacin, lomefloxacin, norfloxacin, pefloxacin. sparfloxacin. and temafloxacin. The minimum inhibitory concentrations (MIC) of CI-990 in mg/L required for >90% isolates were 0.03-0.5 for members of *Enterobacteriaceae*, 0.12-2.0 for *Pseudomonas aeruginosa*, 0.03-1.0 for *Aeromonas hydrophila*, 1.0-2.0 for *Acinetobacter calcoaceticus*, 0.5-2.0 for *Brucella melitensis*, 0.06-1.0 for staphylococci, and 1.0-2.0 for enterococci. Its antibacterial activity was comparable or superior to other fluoroquinolones tested against most gram-negative and gram-positive bacteria, including enterococci.

Fluoroquinolones are synthetic, broad spectrum, bactericidal chemotherapeutic agents which inhibit the supercoiling activity of the enzyme desoxyribonucleic acid-gyrase in susceptible bacteria. The fluoroquinolones that have been approved for clinical use in the USA and Europe have excellent antibacterial activity against most gram-negative pathogens, including members of *Enterobacteriaceae* and *Pseudomonas aeruginosa* [1-4]. Although both *Staphylococcus aureus* and coagulase-negative staphylococci are usually susceptible to these drugs, streptococci and enterococci are generally more resistant [2,4-6]. Since structural changes of the parent compound could result in broadening the spectrum of antibacterial activity against gram-positive bacteria while retaining good activity against gram-negative organisms, a number of new fluoroquinolones, such as sparfloxacin and temafloxacin have been developed. CI-990 is a new investigational fluoroquinolone (Figure 1), which is the prodrug of active quinolone PD 131628 and being developed by Parke-Davis Pharmaceutical Research Division. It has been found to be highly effective in acute, systemic experimental mouse infections caused by not only gram-negative bacteria, but being 8-10 times more effective than ciprofloxacin against streptococci [7]. In this paper we report the antibacterial activity of this fluoroquinolone against recent clinical isolates and compare it with six other drugs of its class.

Material and Methods

The bacterial strains used in this study were isolated from patients at the King Faisal Specialist

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From the Department of Pathology and Laboratory Medicine. King Faisal Specialist Hospital and Research Centre, Riyadh.

Address reprint requests and correspondence to Dr. Qadri: King Faisal Specialist Hospital and Research Centre, Head, Section of Microbiology, Pathology, MBC-10, P.O. Box 3354, Riyadh 11211, Saudi Arabia

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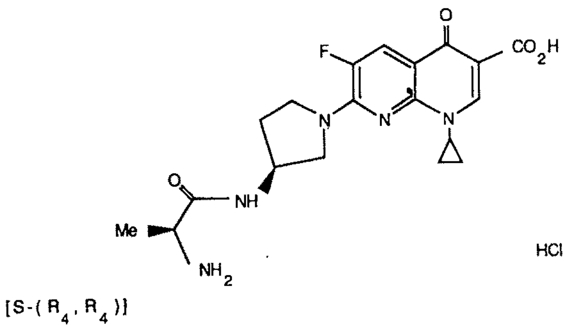

FIGURE 1. Chemical structure of CI-990 (Chemical Data Sheet, Warner-Lambert/Parke-Davis Pharmaceutical Research Division).

Hospital and Research Centre (KFSH & RC), a 550-bed tertiary care facility that serves as a referral hospital for the Kingdom of Saudi Arabia and the Middle East. All the microorganisms were identified by standard methods as described in the Manual of Clinical Microbiology [10]. All the strains were stored at 4°C in trypticase soy broth (BBL, Cockeysville, MD, USA) until use.

CI-990, CI-960, and sparfloxacin were obtained from Parke-Davis Pharmaceutical Research Division (Ann Arbor, MI, USA), and temafloxacin from Abbott Laboratories (North Chicago, IL, USA). Other drugs were purchased from commercial sources. All the drugs were stored, dissolved, and diluted as per recommendations of the manufacturer or those of the National Committee for Clinical Laboratory Standards [8].

Antimicrobial susceptibility testing was performed for all bacteria except *Brucella* melitensis by the agar dilution method as per NCCLS [8] recommendations. Inoculum was prepared from 18-24 h cultures grown on trypticase soy agar or 5% (v/v) sheep blood agar. The bacterial suspensions were adjusted to contain 10^7 CFU/ml and spot inoculated to contain 10^4 CFU per spot onto the agar surface with a multipoint inoculator. Mueller-Hinton agar (BBL, Cockeysville, MD, USA) and pH 7.2-7.4 were used throughout the study. All incubations were at 35°C for 18-24 h. *Escherichia coli* ATCC 25922, *Pseudomonas-aeruginosa* ATCC 27853 and *Staphylococcus aureus* ATCC 29213 were used as quality control organisms. The quality control results were found to be within expected ranges [8] during the period of investigation. Bacteria were considered resistant when the MICs for fluoroquinolones were $\geq$4.0 mg/L [2,8-10].

Minimum inhibitory concentrations of the fluoroquinolones and other antimicrobials against *Brucella* were determined by agar dilution method according to the standard method [8,11]. The medium used was Meuller-Hinton II agar (BBL, Cockeysville, MD, USA) which was supplemented with 5% sheep blood. The bacterial suspensions were adjusted to contain 10,000,000 CFU/ml and spot inoculated to contain 10,000 CFU/spot onto the agar surface with a multipoint inoculator. All incubations were at 35°C for 48 h in a CO_2 incubator. Sparfloxacin, CI-960 and PD 131628 were obtained from the Parke-Davis Pharmaceutical Research Division (Ann Arbor, MI, USA); temafloxacin from Abbott Laboratories (Abbott Park, IL, USA) and lomefloxacin from Searle (Skokie, IL, USA). All other agents were purchased from commercial sources.

Results

Of the 1021 bacterial isolates used in this comparative in vitro activity of CI-990, members of *Enterobacteriaceae* constituted 444 strains, 114 pseudomonads, 104 *B. melitensis*, 52 other gram-negative bacilli, 245 staphylococci, and 54 isolates of enterococci. The antibacterial activity of this drug and those of other fluoroquinolones against *Enterobacteriaceae* is shown in Table 1. More than 90% of the *Enterobacteriaceae* were inhibited by 0.03-0.5 mg/L of CI-990. One isolate of *E. coli*, 2 of *K. pneumoniae*, 2 of *Citrobacter*, and one of *Serratia marcescens* which had MICs of >4.0 mg/L for CI-990 also showed cross-resistance to various other fluoroquinolones.

Its activity against *Acinetobacter* was comparable to ciprofloxacin and lomefloxacin, inferior to CI-960, sparfloxacin and temafloxacin, but superior to fleroxacin and pefloxacin (Table 2). All strains of *A. hydrophila* tested and 2 isolates each of *Achrombacter xylosoxidans*, *Weeksella*, and *Rahnella* (not shown in Table 1) were inhibited by 0.03-1.0 mg/L of CI-990. All the 104 isolates of *B. melitensis* shown in Table 1 responded in vitro to 0.5-2.0 mg/L of CI-990. One of the isolates from a patient with acute discitis developed resistance to ciprofloxacin with an MIC of >4.0 mg/L, while under treatment with this drug [12-14]. The parent strain was susceptible to ciprofloxacin, CI-990 and

Table 1. *In vitro activity of CI-990 and other flouroquinolones against Enterobacteriaceae.*

Organism	Drug**	MIC mg/L			Susceptible %
		MIC_{50}	MIC_{90}	Range	
E. coli (106)	CI-990	0.25	0.5	0.03->4.0	99
	CI-960	<0.03	<0.03	0.03-0.12	100
	Ciprofloxacin	<0.03	0.12	0.03-0.5	100
	Fle, Lome	0.12	1.0	0.12->4.0	99
	Norfloxacin	<0.03	<0.03	<0.03-0.12	100
	Pefloxacin	0.12	2.0	0.12->4.0	99
	Tema, Spar	0.06	0.25	0.03->4.0	99
Klebsiella pneumoniae (53)	CI-990	0.5	2.0	0.12->4.0	97
	CI-960	<0.03	0.12	<0.03->4	98
	Ciprofloxacin	<0.03	0.25	0.06-0.25	98
	Lomefloxacin	0.25	1.0	0.25->4.0	97
	Nor, Pef, Fle	0.12	2.0	0.12->4.0	97
	Sparfloxacin	0.06	0.5	<0.03->4	98
	Temafloxacin	0.12	0.12	<0.12->4	97
Klebsiella oxytoca (15)	CI-990	0.5	2.0	0.12-4.0	100
	CI-960	<0.03	0.12	<0.03-0.12	100
	Ciprofloxacin	0.06	0.25	0.06-0.5	100
	Fleroxacin	0.12	0.5	0.12-1.0	100
	Lomefloxacin	0.12	0.25	0.12-0.5	100
	Nor, Pef	0.25	0.5	0.25-2.0	100
	Sparfloxacin	0.03	0.5	<0.03-0.5	100
	Temafloxacin	0.12	0.5	<0.06-1.0	100
Enterobacter sp. (64)	CI-990	0.12	0.5	0.12-4.0	100
	CI-960	<0.03	0.12	<0.03-0.5	100
	Ciprofloxacin	0.12	2.0	0.12-4.0	100
	Fle, Pef	0.12	1.0	0.12->4.0	95
	Lomefloxacin	0.12	2.0	0.12->4.0	97
	Norfloxacin	0.05	2.0	0.05->4.0	95
	Spar, Tema	0.03	0.12	<0.03-1.0	100
Citrobacter sp. (25)	CI-990, Fle	0.12	1.0	0.12->4.0	92
	CI-960	<0.03	0.12	<0.03-0.12	100
	Ciprofloxacin	0.06	0.5	0.06-1.0	100
	Lome, Pef	0.12	1.0	0.06-1.0	100
	Norfloxacin	0.25	2.0	0.12-2.0	100
	Sparfloxacin	<0.03	>4.0	<0.03->4.0	83
	Temafloxacin	0.5	>4.0	<0.03->4.0	83
Serratia marcescens (30)	CI-990	0.5	1.0	0.12->4.0	97
	CI-960	<0.03	0.12	<0.03-0.12	100
	Ciproloxacin	0.25	0.5	0.12-0.5	100
	Fleroxacin	0.5	>4.0	0.12->4.0	83
	Lomefloxacin	0.5	1.0	0.06-1.0	100
	Nor, Pef	0.5	2.0	0.25->4.0	97
	Spar, Tema	0.12	1.0	0.03-4.0	100
Proteus sp. (40)	CI-990	1.0	2.0	0.12-4.0	100
	CI-960	<0.03	0.52	<0.03-0.12	100
	Cipro, Fle, Lome	0.25	0.5	0.12-1.0	100
	Nor, Tema	0.5	2.0	0.5->4.0	98
	Pefloxacin	0.12	1.0	0.12->4.0	98
	Sparfloxacin	0.12	1.0	0.03-4.0	100
Morganella marganii (31)	CI-990	0.25	1.0	0.12-4.0	100
	CI-960	<0.03	0.12	<0.03-0.12	100
	Cipro, Fle	0.12	0.25	0.06-0.5	100
	Lomefloxacin	0.25	0.25	0.12-0.5	100
	Nor, Pef	0.25	1.0	0.25-1.0	100
	Spar, Tema	0.12	0.5	0.06-0.5	100
Salmonella sp. (44)	CI-990	0.12	0.5	0.03-0.5	100
	CI-960	<0.03	0.03	<0.03-0.06	100
	Cipro, Fle, Lome	0.06	0.25	0.06-0.5	100
	Nor, Pef	0.25	0.5	0.12-1.0	100
	Spar, Tema	0.06	0.12	0.03-0.12	100

Table 1. *Continued.*

Organism	Drug**	MIC mg/L			Susceptible %
		MIC_{50}	MIC_{90}	Range	
Shigella *sp.* (36)	CI-990	0.12	0.5	0.12-0.5	100
	CI-960	<0.03	0.12	<0.03-0.12	100
	Ciprofloxacin	0.06	0.12	0.06-0.25	100
	Fle, Lome	0.12	0.5	0.12-0.5	100
	Nor, Pef	0.25	1.0	0.25-1.0	100
	Spar, Tema	0.06	0.12	0.03-0.12	100

* Abbreviations used in Tables 1, 2 & 3: cipro = ciprofloxacin; fle = fleroxacin; lome = lomefloxacin; spar = sparfloxacin; pef = pefloxacin; tema = temafloxacin; nor = norfloxacin.

TABLE 2. *Comparative antibacterial activity of CI-990 against other Gram negative bacteria.*

Bacterium	Drug**	MIC mg/L			Susceptible %
		MIC_{50}	MIC_{90}	Range	
Acinetobacter *sp.* (26)	CI-990	1.0	2.0	1.0->4.0	96
	CI-960	<0.03	1.0	<0.03-1.0	100
	Cipro, Lome	0.25	1.0	0.25->4.0	96
	Fleroxacin	0.5	2.0	0.12->4.0	77
	Nor, Pef	0.5	>4.0	0.5->4.0	69
	Spar, Tema	<0.03	0.12	<0.03-0.12	100
Pseudomonas *aeruginosa* (98)	CI-990	1.0	2.0	0.12->4.0	95
	CI-960	0.12	0.5	0.12-0.5	100
	Cipro, Lome	0.5	2.0	0.5->4.0	96
	Fleroxacin	0.5	2.0	0.5->4.0	89
	Lomefloxacin	0.5	2.0	0.5->4.0	93
	Nor, Tema	1.0	2.0	0.5->4.0	95
	Pef, Spar	1.0	4.0	0.5->4.0	89
Pseudomonas *sp.* (16)	CI-990	0.5	>4.0	0.5->4.0	67
	CI-960, Cipro	0.06	0.5	0.06-1.0	100
	Fle, Lome	0.5	>4.0	0.5->4.0	67
	Nor, Pef	1.0	>4.0	0.5->4.0	62
	Spar, Tema	0.5	2.0	0.5->4.0	94
Aeromonas *hydrophia* (26)	CI-990	0.12	1.0	0.03-1.0	100
	CI-960	<0.03	0.03	<0.03-0.06	100
	Cipro. Lome	0.06	0.25	0.06-0.5	100
	Nor, Pef	0.25	0.5	0.12-1.0	100
	Spar, Tema	0.06	0.12	0.03-0.12	100
Brucella *melitensis* (104)	CI-990	1.0	2.0	0.5-2.0	100
	CI-960, Lome	0.12	0.12	0.06-0.25	100
	Ciprofloxacin	0.25	0.5	0.03-2.0	100
	Nor, Pef, Fle	0.25	0.5	0.12-0.5	100
	Spar, Tema	2.0	2.0	2.0	100

other fluoroquinolones with an MIC of 0.06-2.0 mg/L. However, the strain which required resistance to ciprofloxacin remained resistant to all other fluoroquinolones, including CI-990, with an MIC of >4.0 mg/L.

Over 97% methicillin-susceptible and methicillin-resistant S. aureus as well as coagulase-negative staphylococci were inhibited by 0.06-2.0 mg/L of CI-990 (Table 3). This was the most effective drug against enterococci, inhibiting 96% of the 54 strains as compared to 28% for pefloxacin, 31% for norfloxacin, 37% for CI-990 and fleroxacin, and 48% for ciprofloxacin.

Discussion

1,8-Napthyridine-3-carboxylic acid, CI-990, is a recently developed investigational fluoroquinolone with the empirical formula of $C_{19}H_{22}$ $FNSO_4$ HCl and molecular weight of 454.29 (Chemical Data Sheet, Warner-Lambert/Parke-Davis Pharmaceutical Research Division). Its development came about as part of an effort to synthesize a fluoroquinolone with extended activity against organisms, such as enterococci, which are notoriously resistant to almost all the fluoroquinolones developed thus far, with the exception of sparfloxacin [1,5,15,16]. The

TABLE 3. *In vitro activity of fluoroquinolene against Gram-positive cocci.*

Organism (n)	Drug	MIC mg/L MIC$_{50}$	MIC$_{90}$	Range	Susceptible %
Staphylococcus aureus, methicillin susceptible (91)	CI-990. Lome	0.5	1.0	0.12-2.0	100
	CI-960	<0.03	<0.03	<0.03	100
	Ciprofloxacin	0.25	1.0	0.12-1.0	100
	Nor, Pef, Fle	0.5	1.0	0.25-2.0	100
	Sparfloxacin	0.12	0.5	0.12-0.5	100
	Temafloxacin	0.25	0.5	0.12-1.0	100
Staphylococcus aureus, methicillin resistant (31)	CI-990	1.0	1.0	0.5-2.0	100
	CI-960	<0.03	<0.03	<0.03	100
	Cipro, Tema	0.25	1.0	0.12-1.0	100
	Fleroxacin	0.5	2.0	0.25-2.0	100
	Lome, Pef	0.25	1.0	0.12-2.0	100
	Norfloxacin	0.5	1.0	0.25-2.0	100
	Sparfloxacin	0.12	0.5	0.12-0.5	100
Coagulase negative staphylococci (123)	CI-990	0.5	1.0	0.06->4.0	94
	CI-960	<0.03	0.12	<0.03	100
	Ciprofloxacin	0.5	2.0	0.5-4.0	100
	Lome, Nor, Fle, Pef	1.0	2.0	0.5->4.0	92
	Spar, Tema	0.25	2.0	0.12->4.0	94
Enterococcus (54)	CI-990	1.0	2.0	1.0->4.0	96
	CI-960, Fle, Nor	>4.0	>4.0	2.0->4.0	37
	Cipro, Tema	0.5	4.0	0.5->4.0	82
	Lomefloxacin	>4.0	>4.0	2.0->4.0	43
	Pefloxacin	>4.0	>4.0	2.0->4.0	28
	Sparfloxacin	2.0	2.0	0.5->4.0	92

present study shows that CI-990 has excellent activity against a wide range of bacterial isolates from clinical specimens. Its potency against most of the *Enterobacteriaceae* was comparable to not only investigational fluoroquinolones but to those approved for use in clinical practice. The same was true of other gram-negative bacteria that included *P. aeruginosa, Acinetobacter, Aeromonas hydrophila* and intracellular pathogens such as *B. melitensis.*

Like other fluoroquinolones, CI-990 was very effective against both methicillin-resistant and methicillin-susceptible *S. aureus* as well as coagulase-negative staphylococci. However, unlike other fluoroquinolones, it had excellent activity against enterococci, inhibiting 96% of the 54 strains tested at an MIC of 1-2 mg/L, followed by sparfloxacin with 92% and temafloxacin inhibiting 82% of the isolates. The remaining fluoroquinolones had little activity against this organism. Pharmacokinetic studies have shown that CI-990's active drug PD 131628 is released rapidly upon oral or parenteral administration in experimental animals and has excellent absorption and distribution properties [19].

Although the bacteria used in this study are relatively more resistant to commonly used antimicrobials as compared to their counterparts in USA [17,18], CI-990 demonstrated excellent in vitro activity against a wide variety of both gram-positive and gram-negative bacteria. We believe that further studies are warranted to establish the clinical usefulness of this new fluoroquinolone.

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CAMPYLOBACTER JEJUNI ENTEROCOLITIS IN NEONATES

AKM Harunur Rashid, MRCP (UK), DCH; Hussein Salman, MD;
Mohamed Istiaque Hussain, MBBS; Saad Mohammed Al-Hadlaq, Facharzt

تعتبر الكامبيلوباكتر الصائمية من أهم الجراثيم الممرضة إحداثاً للالتهاب الحاد في السبيل المعدي المعوي لدى الأطفال. لم تصف النشرات الطبية العالمية إلا بضع حالات من الالتهاب المعوي القولوني لدى الولدان بسبب الكامبيلوباكتر، ولم تكن أي منها من المملكة العربية السعودية. نصف في هذا المقال ست حالات من حالات الالتهاب المعوي القولوني في المواليد بسبب هذه الجرثومة والتي تم عزلها خلال الفترة من شهر سبتمبر ١٩٨٩م إلى شهر يناير ١٩٩١م في مستشفى الأطفال في السليمانية، الرياض، المملكة العربية السعودية حضر جميع المرضى بسبب إصابتهم بالإسهال لفترة تتراوح بين يوم واحد إلى عشرين. لوحظ وجود دم في براز ثلاثة من المرضى ، بينما لوحظ مخاط في براز اثنين منهم. وخلافاً لمشاهدات باحثين آخرين، حضر خمسة مواليد بسب الإصابة بالحمى. عولج أحد المواليد بالإريثرومايسين، وتلقى مولد آخر الأوغمنتين بينم تلقى اثنان صادات أخرى للاشتباه بإصابتهما بالإنتان. تم إيقاف إعطاء الصادات السابقة وإضافة الإريثرومايسين لمريض واحد، ولم يتلق اثنان أية صادات. يجب الاشتباه بالكامبيلوباكتر في أي مولود يحضر إلى المستشفى بسبب الإسهال المصحوب بمخاط ودم في البراز.

Campylobacter jejuni is one of the leading bacterial pathogens causing acute gastroenteritis in children. Only a few cases have been described in the world literature about neonatal enterocolitis due to campylobacter and none from Saudi Arabia. We describe six cases of neonatal enterocolitis due to this organism isolated during the period from September 1989 - January 1991 at Suleimania Children's Hospital, Riyadh, Saudi Arabia. All of the patients presented with diarrhea; duration ranging from 1-20 days. Three patients had blood and two had mucus in their stool. In contrast to the findings of other investigators, five neonates presented with fever. One neonate was treated with erythromycin, another received augmentin, and two received other antibiotics because of suspected sepsis. In one patient, previous antibiotics were discontinued and erythromycin was added and two received no antibiotics. Campylobacter infection should be suspected in any neonate presenting with diarrhea accompanied by mucus and blood in the stool.

Since 1977 [1], campylobacter fetus ss jejuni has been recognized as a leading bacterial enteropathogen causing gastroenteritis in humans. In 1979 [2], this came into focus as a pediatric enteropathogen. Campylobacter can be cultured from 3-11% of patients with diarrhea. This is a recovery rate comparable to or exceeding that of Shigella or Salmonella species [3]. Only a few cases have been reported in the world literature [4-8], with no literature originating from Saudi Arabia or any Middle Eastern country. We have identified six cases of neonatal campylobacter enterocolitis at Suleimania Children's Hospital in Riyadh, Saudi Arabia from September 1989 - January 1991. We describe the clinical features and other findings of these neonates.

Material and Methods

Stool specimens of neonates admitted in the hospital with diarrhea were cultured for campylobacter in addition to other common enteropathogens as a routine. Specimens were plated on selective campylobacter agar media that contained 5% sheep erythrocytes, vancomycin, polymyxin, cephalothin, and amphotericin B (Campy-5) prepared by Saudi Prepared Media Ltd., Riyadh.

From the Department of Pediatrics, Suleimania Children's Hospital, Riyadh.
Address reprint requests and correspondence to Dr. Rashid: P.O. Box 59046, Riyadh 11525, Saudi Arabia.
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Campylobacter agar plates were incubated at 42-43°C in 5% O_2, 10-12% CO_2 in anaerobic jars with commercial gas generating system (BBL, Gaspak Anaerobic System), examined at 24, 48, and 72 h. Cultures were confirmed later for campylobacter jejuni by colony character, gram staining, and biochemical characteristics [9]. Sensitivity to antibiotics was tested by disc diffusion method.

We reviewed the medical records of neonates admitted to the hospital whose stool cultures yielded campylobacter jejuni. Findings were tabulated for the presence of fever, vomiting, signs of dehydration, information about diarrhea, complete blood count, serum electrolytes, blood urea nitrogen, creatinine, and results of blood and spinal fluid cultures, if performed.

Results

All six neonates were delivered vaginally at term without any perinatal problems. Three were Saudi and the remaining three neonates, non-Saudi. Age on presentation ranged from 17-27 days. Age at onset of diarrhea was 5-26 days (Table 1); five were female, two neonates (Cases 2 and 3) vomited for 3 and 14 days, respectively, 2-3 times per day. Three neonates had bloody (Cases 1,4, and 5), two had mucoid (Cases 3 and 6), and one neonate presented with watery stools. On presentation, the duration of diarrhea was 1-20 days with a frequency ranging from 5-12 times a day. Two neonates had mild dehydration and the remaining neonates were well hydrated. Four presented with temperatures ranging between 37.5-38.5°C, one had a temperature of 39°C and one neonate was afebrile. Within 24 h of admission, fever subsided in all the neonates. None had abdominal distention, two looked ill (Cases 2 and 3), and one neonate had impetigo (Case 3). Three patients (Cases 2, 5, and 6) were irritable on admission. Body weight ranged from 2.8 to 4.5 kg and mean was 3.87 kg. Three children were fed breast milk since birth, two were on bottle feeding, one was on the breast and artificial feeding.

Investigations

Lumbar puncture was performed in two (Cases 2 and 3), and spinal fluid examination was normal. Blood was cultured in two (Cases 2 and 3), which yielded no growth. Serum electrolytes, blood urea nitrogen, and creatinine were performed in all neonates. One had hypernatremic dehydration with prerenal failure (Case 2). The child was fed on concentrated artificial milk powder and improved with conservative treatment.

Peripheral WBC counts were performed on all. WBC count ranged from 7.6x10^9/L - 17.6x10^9/L, neutrophil count 20-65%, lymphocytes 27-83%, monocytes 1-6%, blood urea nitrogen 1.2-10.2 mmol/L, and creatinine 37-44 umol/L.

Culture sensitivity report revealed campylobacter jejuni was sensitive in all the cases to erythromycin, augmentin, gentamicin, and nalidixic acid, but resistant in all to trimethoprim + cotrimoxazole. Ampicillin was sensitive to all except in one patient (Case 3).

Treatment

One neonate, (Case 4), received oral rehydration solution (ORS) and the remaining received parenteral fluid (IVF). All patients were discharged home following improvement; hospital stay was 3-14 days. Two neonates (Cases 4 and 6) did not receive any antibiotics. Diarrhea improved after two days in both

TABLE 1. *Clinical and laboratory features of six neonates with campylobacter gastroenteritis.*

Patient/Age in days/Sex	Wt. (kg) of baby	Feeding	Age at onset of diarrhea or bloody stool (days)	Duration of diarrhea (days*)	Dehydration	Temp. on admission (oC)	WBC/ cumm	Hospital stay (days)
1/25/F	4.5	B+A	23	2	-	37.8	14,200	5
2/18/F	2.8	A	15	3	+	38.2	17,600	9
3/17/F	3.0	A	15	2	+	38.5	14,600	14
4/26/M	4.2	B	25	1	-	39	8,800	3
5/27/F	4.2	B	26	1	-	37	7,600	3
6/25/F	4.5	B	5	20	-	38.1	10,600	3

F = female ; M = male; BF = breastfeeding; A = artificial feeding; (+) symbol = present; (-) symbol = absent;
* Prior to admission.

patients who were later discharged with follow-up advice. Culture reports were available after discharge, but the patients were lost to follow up. Erythromycin and augmentin were administered for two neonates (Cases 1 and 5) on the fourth and second day of hospitalization, respectively, upon the arrival of the stool culture report. Diarrhea improved in Case 1 on the third day, one day prior to administering erythromycin and the baby was discharged on the following day. In Case 5, diarrhea stopped on the third day, one day after the initiation of augmentin and the baby was discharged the following day. Ampicillin with gentamicin and cloxacillin with cefuroxime were administered in Cases 2 and 3, respectively, on admission because of suspected neonatal sepsis. Septic screening was carried out on both patients which was found to be negative. Campylobacter isolated from Case 2 was sensitive to both ampicillin and gentamicin and they were continued for nine days, at which time the diarrhea improved after two days. Repeated stool culture on the sixth day of admission was negative for campylobacter or any other bacterial enteropathogens.

A stool culture report on Case 3 was obtained two days later. With this, erythromycin was added on the third day and cloxacillin and cefuroxime were discontinued. Erythromycin syrup was administered for seven days, but the diarrhea continued for 11 days. A stool culture was repeated nine days after starting erythromycin and was negative. The patient was discharged home on the 14th day in good condition. Stool specimens of parents and siblings were not screened for campylobacter. During this study period, campylobacter was cultured from stools of neonates with diarrhea more often than either Salmonella or Shigella. No secondary case was reported in our nursery.

Discussion

Campylobacter has been known to cause perinatal infection in humans for a long period of time. In 1979, Torphy and Bond [10] reported on 12 neonates with campylobacter infection. Two of the newborns had bloody diarrhea [10]. Since then, Karmali and Tan described one neonate in 1980 [4], and in 1981, Anders et al, [5]. reported eight cases of neonatal gastroenteritis due to campylobacter fetus ss jejuni infection. In 1977 a brief epidemiologic report from Britain described nine neonates with gastroenteritis without providing a detailed report [11]. Four additional cases of neonatal enterocolitis were described in a neonatal unit in 1984 by Karmali et al [7]. In 1985, Young et al [8], reported on three cases. This was also described in premature babies [12,13]. Thus far, we know of no cases having been reported from Saudi Arabia or any Middle Eastern country.

In contrast to the findings of previous reports [7, 14, 15], 5/6 of our neonates were febrile. Two babies had mild dehydration which may have contributed to the pyrexia. Older children may have associated fever which has been documented in previous studies [15,16] and may even present with convulsions [17]. None had abdominal distention. Monocyte count ranged from 0-6%. We did not encounter any cases involving meningitis or septicemia due to campylobacter jejuni during this period, although they have been recorded in earlier reports [18-21]. Campylobacter may frequently be associated with diarrhea in immunodeficient children [22]. Cases involving severe arthritis with campylobacter were also reported [23].

The transmission of campylobacter is through the fecal-oral route or person-to-person contact. Natural reservoirs of campylobacter include: surface water, wild and domestic animals including fowl, cattle, dogs, and cats [24]; outbreaks associated with raw milk and drinking water have also been reported [25-27]. In this study we did not try to look for the source of campylobacter and route of transmission. Erythromycin is regarded as the drug of choice since Vanhoof's report in 1980 [28]. Salazar-Lindo et al [29] demonstrated that erythromycin shortens the duration of diarrhea if started early in the treatment plan. It also appears from other studies that erythromycin decreases the fecal excretion time for campylobacter [30,31]. This may be important from an epidemiological point of view in decreasing intrafamilial spread [15]. We treated one neonate with erythromycin after receiving a stool culture sensitivity report when his diarrhea had already improved. We treated another neonate with augmentin (amoxicillin + clavulinic acid) as it is also a satisfactory regime in our experience at Suleimania Children's Hospital. We did not encounter any resistance to this drug for this organism. Although erythromycin is the preferred drug for campylobacter jejuni enterocolitis, resistance has been reported which reached 13.4% in Taiwan [32].

We conclude that campylobacter jejuni should be sought in stool specimens of newborns with diarrhea, particularly if the diarrhea is bloody or mucoid. The neonates may present with or without fever. To learn more about the risks of severe enterocolitis, bacteremic complications or secondary spread in nurseries, further studies should be conducted on infected neonates. Additional studies are required to be conducted in a prospective fashion in this part of the world in order to understand the epidemiological factors related to campylobacter infection during the perinatal period.

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Special Communications

HEGIRA ADAPTATION OF THE NCHS WEIGHT AND HEIGHT CHARTS

Magued I. Osman, PhD; Gady Magbool, Facharzt; Kanwar K. Kaul, MD

يتم تسجيل واحتساب أعمار الأطفال السعوديين على أساس التقويم الهجري. ولدى تسجيلهم في سجلات المركز الوطني للإحصاءات الصحية الخاصة بالوزن والطول يتعرضون للغبن لأن السنة الهجرية أقصر من السنة الميلادية. قدرت هذه الدراسة النسب المئوية للطول والوزن المستقاة من مراجع المركز الوطني للإحصائيات الصحية والمعدلة باستخدام الاستيفاء الرياضي بالنسبة للعمر بالسنوات الهجرية لمن تتراوح أعمارهم بين ١٢ و ٢٨ عامًا هجريًا. أعدت السجلات لتطبيقها في المستشفيات والمراكز الصحية على الأطفال الذين سجلت أعمارهم بالتقويم الهجري.

The ages of Saudi children are recorded and based on the Hegira calendar. When charted on the National Center for Health Statistics (NCHS) weight and height charts, children will be at a disadvantage since the Hegira year is shorter than the Gregorian year. In this paper, centiles for the NCHS reference population are estimated for age in Hegira years from 2-18 for height and weight for both sexes using mathematical interpolation. Charts are prepared for use in hospitals and health centers for children whose ages have been reported based on the Hegira calendar.

During a study of growth in weight and height of Saudi children in the Eastern Province by Magbool et al (in press) [1], it was observed that the ages of children had been recorded by parents and school authorities according to the Hegira calendar which is comprised of a 354-day (Lunar) year as opposed to 365 days in the Gregorian year. Since the Hegira year is shorter by 11 days, a child reported to be 15 years of age will be instead 14-years and 6.5 months based on the Gregorian year. When charted on the National Center for Health Statistics (NCHS) weight and height charts (National Center for Health Statistics 1977) [2], this child will be at a disadvantage as he is being compared with a child nearly six months older on the international reference standard. Thus, for a valid comparison, two alternatives were made available to us: (1) to adapt the NCHS charts to the Hegira year, and (2) convert each child's age from the Hegira to the Gregorian year. With a large data of over 20,000 children, the first alternative was strongly preferred.

Method

Interpolation has been applied to NCHS growth curves to derive expected heights and weights for ages based on the Hegira year. The following equations have been derived for this purpose: $HTH(n)=HTG(n-1) + [HTG(n) - HTG(n-1)] \times [n-(n-1)f]/f$ where $HTH(n)$ is the height in Hegira years for a boy or girl who is n-year old. $HTG(n-1)$ is the height in Gregorian years for a boy or girl who is (n-1) year old. $HTG(n)$ is the height in Gregorian years for a boy or girl who is n-year old, and f is the number of Hegira years in one Gregorian year (=365/354).

Similarly, $WTH(n)=WTG(n-1)+[WTG(n)-WTG(n-1)] \times [n-(n-1)f]/f$ where $WTH(n)$ is the weight in Hegira years for a boy or girl who is n-year old. $WTG(n)$ is the weight in Gregorian years for a boy or girl who is n-year old, $WTG(n-1)$ is the weight in Gregorian years for a boy or girl who is n-1 year old, and f is the number of Hegira years in one Gregorian year (=365/354).

The derivation is based on the assumption that the height or weight between any two consecutive Gregorian years from 2-18 and between any two

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From the Department of Family and Community Medicine (Dr. Osman), and the Department of Pediatrics (Drs. Magbool and Kaul), King Faisal University, College of Medicine and Medical Sciences, Dammam.

Address reprint requests and correspondence to Dr. Magbool: Associate Professor, King Faisal University, College of Medicine and Medical Sciences, P.O. Box 2114, Dammam 31451, Saudi Arabia.

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consecutive six month periods from 18-36 months is a straight line. Interpolation for younger children was performed on six month intervals since the younger the child, the higher the height or weight velocity will be. For example, the median height will increase according to NCHS curves by 25.6 cm, 11.5 cm, 8.9 cm, and 8.00 cm during the first four years of life. A similar trend persists among females and applies to height as well as weight.

Results and Discussion

These calculations, performed using EPI software, Dean et al [3], are presented in Figures 1 and 2 and cover ages 2-18 for both sexes. These figures are prepared for use in hospitals and primary health care units. We recommend that communities in which age is reported in Hegira years use these adapted figures and not rely on charts based on the Gregorian year. By doing so, the expected 50th centile for height and weight of a 10-year-old boy based on the Hegira year is over-estimated by 6.1 cm and 1.0 kg, respectively. The amount of over-estimation increases with velocity and age, so that the expected 50th centile for height and weight for 16-year-old boys (Hegira year) will be over-estimated by 2.2 cm and 2.69 kg if the calculations based on the Gregorian year are used, thus placing the child at a disadvantage. We, therefore, recommend that the Hegira adaptation of the NCHS figures presented in this brief communication be utilized in hospitals and health centers in countries using the Hegira calendar until such time as an indigenous reference standard is made available.

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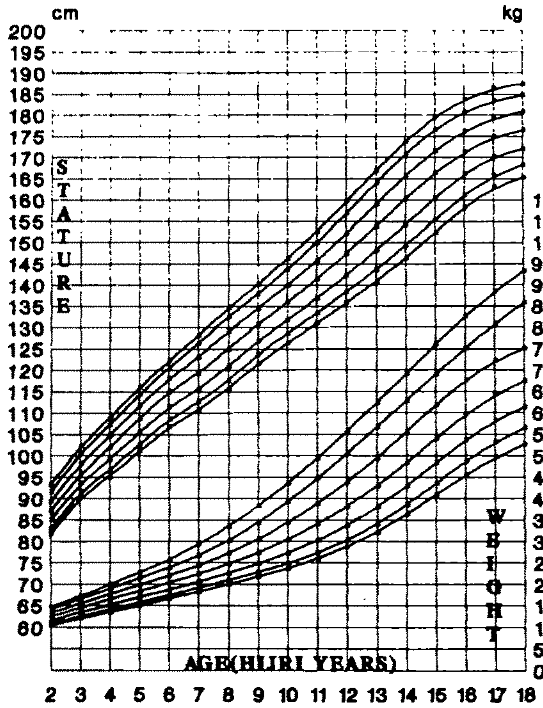

FIGURE 1. Adapted NCHS weight and height charts to be used for boys whose ages have been reported based on the Hegira calendar.

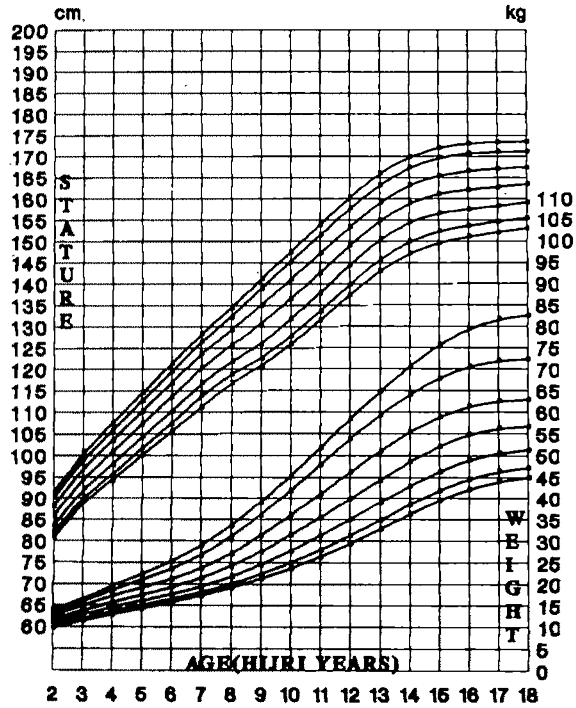

FIGURE 2. Adapted NCHS weight and height charts to be used for girls whose ages have been reported based on the Hegira calendar.

PRESCRIBING PATTERNS OF AMBULATORY CARE PHYSICIANS IN SAUDI ARABIA

Saleh A. Bawazir, PhD

قمنا بدراسة أنماط وصف العقاقير من قبل الأطباء لمراجعي مستشفيات وزارة الصحة وذلك من خلال مراجعة عينة مؤلفة من ١٠,٢٩١ من الوصفات الطبية التي حصلنا عليها من اثنين وعشرين مستشفى عاما تغطي مناطق مختلفة للخدمات الطبية في المملكة العربية السعودية. أظهر تدقيق هذه الوصفات أن التوثيق بصفة عامة لم يكن كاملاً. فالمعلومات المتعلقة بسن المرضى والتشخيص كانت غائبة في ١٨,٦٪ و٩,٨٪ من الوصفات على التوالي. كان معدل عدد العقاقير في كل وصفة ٢,١ ± ٠,٩٥ كانت أكثر العقاقير وصفًا هي مضادات الأخماج والمسكنات/مضادات الحمى ومستحضرات الفيتامينات على التوالي. وبالتحديد، كان الباراسيتامول والأمبيسيلين والمستحضرات المضادة للحموضة وفيتامين ب أكثر العقاقير وصفًا. تشير الأنماط الملاحظة لاستعمال العقاقير في هذه الدراسة إلى ميل نحو الإفراط في وصف فئات معينة من العقاقير. ناقشنا في هذه الدراسة ضرورة تحسين السياسة الحالية للعقاقير ووصفها ورفعنا توصية لإنشاء وحدة الوبائيات الدوائية لمراقبة استعمال العقاقير في المملكة.

The drug prescribing patterns of ambulatory care physicians in the Ministry of Health (MOH) hospitals were studied by examining 10,291 systematically sampled prescriptions obtained from 22 general hospitals covering the various health regions within Saudi Arabia. An audit of prescription information revealed that documentation was not generally complete. Information relating to patient age and diagnosis was missing in 18.6% and 9.8% of the prescriptions, respectively. The average number of drugs per prescription was 2.1 ± 0.95. The most frequently prescribed drug categories were systemic anti-infectives, analgesics/antipyretics, and vitamin preparations, respectively. Paracetamol, ampicillin, antacid preparations, and vitamin B complex were the specific drugs that ranked high in the frequency of prescription. The patterns of drug use observed in this study indicate a trend for the overprescribing of certain categories of drugs. The need to improve current drug policy and drug prescribing is discussed with a recommendation for the establishment of a Pharmacoepidemiology Unit to monitor drug use in Saudi Arabia.

Since its establishment in the mid 1950s, the health care system within the Kingdom of Saudi Arabia (KSA) has undergone tremendous changes. The process of modernization and expansion of the system was very rapid by all standards [1]. Although the Ministry of Health (MOH) is the main authority responsible for the provision of health care in the country, other government sectors such as the Ministry of Defense, National Guard, and the Ministry of Interior have started providing health care for their employees and dependents. The government health care policy is to provide free health service, including drugs, to all its citizens and resident expatriates. The provision of drugs on a large scale, in addition to ensuring their subsequent proper use, is a massive undertaking for the MOH. Due to this, proper guidelines and adequate controls for drug distribution and appropriate usage need to be developed.

The need to develop a national drug policy and promote rational drug use in Saudi Arabia was recognized early and effective measures to address these issues were undertaken by the passage of two important laws governing the profession of pharmacy and the registration of pharmaceuticals in 1978 [2]. Legislation alone, however, cannot ensure the proper use of drugs. Documentation of drug utilization

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From the Department of Clinical Pharmacy, College of Pharmacy, King Saud University, Riyadh.

Address reprint requests and correspondence to Dr. Bawazir: King Saud University, Department of Clinical Pharmacy, College of Pharmacy, P.O. Box 2457, Riyadh 11451, Saudi Arabia.

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information is an essential step in the process of instituting rational drug use. This issue is a global priority.

The rapid expansion of the pharmaceutical industry in the developed countries in the late 1960s has been responsible for developing countries being flooded with products of both proven and questionable qualities. This, coupled with the industry's intensive advertising campaign in these countries which have weak health education programs, has adversely influenced the pattern of drug use among the population. There is strong evidence of overprescribing and drug misuse with all its societal consequences [3-5]. Overprescribing may be controlled by adhering to basic principles or standards of prescribing drugs. All drug therapy should be effective, safe, appropriate, and economic for the individual being treated. In setting these criteria, there is the understanding that drug therapy constitutes a balance of benefits and risks for the individual receiving treatment [6].

Through proper documentation of prescribing information, identification of healthy and unhealthy drug prescribing practices may be possible and the frequency and importance of adverse drug reactions may also be effectively assessed. Physicians can also use the system to carry out self-audits while health planners can utilize the information to design cost-effective health strategies. The subject of drug prescribing patterns in Saudi Arabia has not been sufficiently studied. The few studies reported to date are limited in their scope and do not reflect the nationwide trend [7-9]. In this report, we discuss the results of prescribing patterns of ambulatory care physicians in general medical and surgical MOH hospitals.

Material and Methods

For the survey, a total of 22 major general medical and surgical hospitals were selected from all the health regions within Saudi Arabia. The selection of these sites was designed to provide a fair reflection on both geographical distribution and population density. The number of samples to be collected was pre-estimated using the standard statistical method to detect any differences in probability value to be within 5% of the true value [10]. This estimate was based on mean drug cost per prescription as a determinant variable, estimated from a pilot study carried out in Riyadh. From these hospitals, a total of 10,291 prescriptions were systematically and continually sampled over a period of 12 months, (January 1988-December 1988), taking into account any seasonal variations in prescribing. To avoid prescriber bias, it was decided to sample prescriptions dispensed during the previous two weeks prior to the researcher's visit. The relative contributions of the different sites to the final sample size were predetermined by proportional allocation method using the number of physicians per hospital as the determinant parameter for size of institution.

After collection, the sampled prescriptions were audited for information relating to patient demography, diagnosis of patient's illness, physician speciality, prescribed drug, dosage form, its strength, dose, frequency, and usage instructions. The resulting data together with unit drug cost were recorded on a specially designed form in numerical codes to facilitate data analysis. The data were fed into the computer and checked for errors. The data were analyzed using the Statistical Package for the Social Sciences (SPSS/PC+). Chi-square test was used to test the differences between parameters.

Results

Out of 10,291 prescriptions analyzed, the ratio of male to female was 1.4. The mean age was 30±16 years (±S.D.) and the difference between male and

TABLE 1. *Age and sex distribution.*

Age of patient	Male No.	Male %	Female No.	Female %	Total No.	Total (%)
<10	736	15.3%	531	15.0%	1267	15.1%
10 - 19	570	11.8%	448	12.6%	1018	12.2%
20 - 29	1230	25.5%	884	24.9%	2114	25.3%
30 - 39	983	20.4%	731	20.6%	1714	20.5%
40 - 49	601	12.5%	458	12.9%	1059	12.7%
50 - 59	352	7.3%	271	7.6%	623	7.4%
>60	351	7.3%	225	6.3%	576	6.9%
Total	4823	100.0%	3548	100.0%	8371	100.0%

Chi-square = 4.79; D.F. = 6; $P = 0.5$.

TABLE 2. *Documentation of prescription information.*

Information Recorded	No.	(%)
Patient Name and Sex		
Present	10269	99.8
Missing	22	0.2
Age of Patient		
Present	8377	81.4
Missing	1914	18.6
Provisional Diagnosis		
Present	9287	90.2
Missing	1004	9.8
Dose		
Specified	20893	95.9
Not Specified	892	4.1
Frequency of Drug Intake		
Specified	20897	95.9
Not Specified	906	4.2
Route of Drug Administration		
Specified	21755	99.9
Not Specified	28	0.1
Dosage Form		
Specified	21767	99.9
Not Specified	18	0.1
Physician Specialty		
Specified	7014	68.2
Not Specified	3277	31.8

female patients was not statistically significant ($P = 0.6$) (Table 1). Table 2 shows the documentation accuracy of prescription information. Physician speciality, patient age, and diagnosis were missing in 31.8%, 18.6%, and 9.8% of prescriptions, respectively. In 4% of the prescriptions, dose of drug and instructions for its use were unspecified. The average number of drugs per prescription was 2.1 ± 0.95. A total of 29% of the prescriptions contained one item, 38.7% contained two items, 25.4 % contained three items, 5.5% contained four items, and 1.3% contained more than four items. The differences between males and females were not statistically significant ($P = 0.5$) (Table 3).

The 20 most commonly prescribed drugs, representing 61.2% of the total prescription items, are shown in Table 4. Paracetamol with 11.2% was at the top of the list followed by ampicillin and antacid preparations with 5.4% and 4.9%, respectively. Table 5 shows the drug category of

TABLE 3. *Number of drugs per prescription.*

Number of drugs	Male		Female		Total	
	No.	%	No.	%	No.	(%)
1	1769	29.5%	1211	28.3%	2980	29.0%
2	2280	38.1%	1697	39.7%	3977	38.7%
3	1535	25.6%	1074	25.1%	2609	25.4%
4	331	5.5%	237	5.1%	568	5.5%
5	56	.9%	48	1.1%	104	1.0%
6	14	.2%	8	.2%	22	.2%
7	5	.1%	4	.1%	9	.1%
Total	5990	100.0%	4279	100.0%	10269	100.0%

Chi-square = 4.36; D.F. = 6; $P = 0.6$.

TABLE 4. *The 20 most commonly prescribed drugs.*

Rank	Drug Name	No.	(%)	Cumulative (%)
1	Paracetamol	2444	11.2	11.2
2	Ampicillin	1182	5.4	16.7
3	Antacid	1067	4.9	21.6
4	Vitamin B complex	1002	4.6	26.2
5	Chlorpheniramine	817	3.8	29.9
6	Ibuprofen	800	3.7	33.6
7	Cough mixture	599	2.7	36.3
8	Aspirin	594	2.7	39.1
9	Multi-vitamin	571	2.6	41.7
10	Hyoscine-N-butybromide (Buscopan)$^{(R)}$	500	2.3	44.0
11	Erythromycin	446	2.0	46.0
12	Vitamin C	445	2.0	48.1
13	Nephazoline and chlorpheniramine eye drops	433	2.0	50.1
14	Co-trimoxazole	391	1.8	51.9
15	Iron preparations	361	1.7	53.5
16	Spasmo-cibalgin$^{(R)*}$	343	1.6	55.1
17	Indomethacin	338	1.6	56.7
18	Chloramphenicol eye ointment	337	1.5	58.2
19	Amoxicillin	328	1.5	59.7
20	Actifed syrup $^{(R)+}$	322	1.5	61.2

R = registered trade name; * = propyphenazone 220mg, allobarbitone 30mg, hexahydroadiphenine HCL 20mg;
+ = triprolidine HCL 2.5mg/10ml, pseudoephedrine HCL 60mg/10ml.

TABLE 5. *Drug category and percent of drug category cost.*

Drug category	No.	%	Percent of drug category cost
Systemic anti-infectives	3358	15.4%	19.9%
Analgesics/Antipyretics	3064	14.1%	1.9%
Vitamins/Minerals	2185	10.0%	4.6%
Eye, ear and nose drugs	1860	8.5%	4.6%
Dermatological drugs	1664	7.6%	10.6%
Antiulcer drugs	1462	6.7%	14.1%
Anti-inflammatory drugs	1343	6.2%	5.6%
Expectorants and antitussives	1103	5.1%	2.9%
Antihistamines	1015	4.7%	1.9%
Antispasmodics	873	4.0%	2.4%
Cardiovascular drugs	676	3.1%	12.4%
Other drugs	636	2.9%	3.1%
Anti-anemics	518	2.4%	1.7%
Anti-asthmatics	427	2.0%	3.9%
Antidiabetics	408	1.9%	5.0%
Laxatives	272	1.2%	.6%
Diuretics	250	1.1%	1.0%
Anti-emetics	214	1.0%	.2%
Antidiarreal drugs	131	.6%	.2%
Antihemorrhoidal drugs	106	.5%	1.9%
Systemic steroids	100	.5%	.3%
Anticoagulants	74	.3%	.8%
Anti-epileptics	46	.2%	.6%
Total	21785	100.0%	100.0%

prescribed drugs and percentage of total drug cost per category. Systemic anti-infectives, analgesics/antipyretics, and vitamins were the most common drug categories prescribed with 15.4%, 14.1%, and 10.0%, respectively. A financial analysis of drug costs revealed that systemic anti-infective drugs accounted for 20%, with anti-ulcer and cardiovascular drugs taking 14% and 12.4% of the total cost, respectively. Moreover, the top three drug categories prescribed represented 26.4% of total drug cost.

Discussion

The results of the present study need to be viewed in light of certain inherent limitations. First, the survey protocol could have been modified to accommodate inter-regional variation and possible seasonal differences within a particular region studied. Practical limitations of finance and manpower have, however, precluded the inclusion of this option in the study. Second, the lack of previous study models on the subject makes it difficult to produce a sound comparative assessment of the present findings. Nevertheless, the study does provide a preliminary data base for the initiation of future comprehensive studies on this subject.

Audits for completeness of prescription information revealed that documentation of information such as patient age, provisional diagnosis, and instructions were incomplete. These findings confirm previous results reported by other investigators [9,11]. An increase in the daily patient load for physicians and the lack of national standards for prescription writing may be responsible for such a practice. A study on prescribing patterns in primary health care in Saudi Arabia have shown that the nursing staff contribute positively to the thoroughness of demographic data for patients and physicians on prescriptions [9].

A total of 32% of prescriptions studied contained three or more drugs and the average number of items prescribed per prescription was 2.1 ± 0.95. This agrees closely with the figures reported for primary health care centers in Saudi Arabia [9], India [11],Yemen [12], and Zimbabwe [13]. However, this figure is lower than the average described in studies conducted in 1980 (3.0) for Saudi Arabia and Ghana [7,14], but greater than that for Singapore (1.8) [15], Italy (1.9) [16], and United States (1.1) [17].

A number of factors have been shown to influence prescribing patterns [16,18-20]. The average number of items prescribed by individual physicians in Saudi Arabia was positively related to the physician's age, average daily patient load, and negatively to the physician's educational background [21]. Although there is a trend toward decreasing the number of drugs prescribed per prescription, current figures remain relatively high, especially when compared with an average of 2-3 medications per patient prescribed for elderly patients with multiple and chronic conditions in the United States [22]. This polypharmacy may be explained by a governmental system which provides free medical service including drugs, a view which is substantiated by a positive correlation between prescription frequency and free medication for the public in the United Kingdom [23] and third-party insurance patients in the United States [24].

Analysis of the 20 most frequently prescribed drugs (Table 4) showed that two-thirds of these drugs are used for symptomatic relief. Paracetamol, ampicillin, antacid, and vitamin B complex were the top four drugs prescribed in Saudi Arabia. In the United States, hydrochlorothiazide, paracetamol, amoxicillin, and erythromycin were the top four drugs prescribed [17]. Seven of the top 20 drugs in this study are also listed among the top 20 drugs prescribed in the United States. The top 20 drugs prescribed comprise 61.1% of drugs prescribed. A similar figure was reported from the United Kingdom and the percentages for Italy, Spain, France, and West Germany varied from 47-35.5% [25].

Furthermore, Table 5 shows that systemic anti-infectives (mostly antibiotics) and analgesics/antipyretics are widely prescribed. This finding confirms a similar pattern reported by researchers in developed [17,25,26] and developing [8-9,11,14] countries. The consequences of overuse and indiscriminate prescribing of antibiotics are well known and have been emphasized extensively in the literature [27-29]. In addition, unwise selection, overprescribing, chronic consumption, and improper storage of analgesics/antipyretics may result in serious adverse reactions [30,31] and accidental poisoning [32].

One may be able to identify prescriptions of developing countries from those of developed countries by the presence of vitamins. Vitamins and minerals ranked third in this study which makes Saudi Arabia no exception to other developing countries [11,14]. Furthermore, three of the 20 most frequently prescribed drugs in this study were vitamins (Table 4). This may indicate that malnutrition is prevalent in Saudi Arabia or vitamins are overprescribed by physicians. The latter seems to be more likely the case. However, it is encouraging to observe that vitamins and minerals ranked third in this study while ranking first in a study conducted in 1985 [8].

Two observations regarding the prescribing patterns of MOH physicians are worth mentioning. The first observation is that ibuprofen is more frequently prescribed as an analgesic/antipyretic in replacement for paracetamol. The second observation relates to the level of prescribing of antacids, antispasmodic, multi-enzyme products which may indicate an increase in the prevalence of gastrointestinal diseases, inadequate eating habits in the general public, or simply overprescribing of medications.

The management of drug expenditure is of great concern to health administrators in developed and developing countries [33,34]. Analysis of drug cost per drug category (Table 5) showed that 20% of the total drug cost is spent on systemic anti-infectives, 14% on anti-ulcer, 12.4% on cardiovascular drugs, 10.6% on dermatological preparations, and 5.6% on anti-inflammatory drugs. Furthermore, 25% of the total drug cost in this study was spent on dermatological preparations and 5.6% on anti-inflammatory drugs. The successful implementation of a specific program or strategy to reduce drug costs at the hospital or national levels will not succeed if it does not consider social, cultural, and market forces, and/or backed up by effective legislation [35]. The process of drug utilization evaluation, which provides feedback regarding personal prescribing patterns to the clinician, offers a way of relaying information which has been subjected to peer judgment and may improve the quality of care. This can be achieved only if the prescriber recognizes that there is a problem and is willing to change his/her prescribing habits [36].

Conclusion

The results of the present study may be of benefit to MOH officials in their overall health policy planning. Such data collection provides baseline data for the drug prescribing patterns in Saudi Arabia. Taking advantage of this insight into current prescribing patterns may provide the possibility of evaluating prescribing practices and in developing policies for drug use. The information and experience gathered from this study are useful elements, serving as a feedback for continuing education programs, which are suitable for integration in daily practice. This study was conducted prior to the full implementation of the primary health care concept designed by MOH, which may allow us to measure the effect of applying such a program on the pattern of drug use in ambulatory care clinics in MOH hospitals. Furthermore, cost analysis figures are imperative for the projection of future drug expenditure. Establishing a sound national drug policy is an integral part of any health care system. Such policy will not serve its purpose if implemented without sufficient information regarding morbidity and mortality data. These data need to be collected and analyzed on a continuous basis and the recommendations and feedback provided to policy makers. To achieve this, MOH and other institutions providing health care services in Saudi Arabia may be able to establish a pharmacoepidemiology or drug utilization unit in cooperation with the Colleges of Pharmacy and Medicine at King Saud University and King Abdulaziz City for Science and Technology (KACST).

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Review Article

THE IMMUNE RESPONSE TO COITUS AND CONCEPTION

Omar Habbal, MB, ChB, PhD; John McLean, MD

من المعلوم أن الخلايا أو الأنسجة المتبادلة بين أفراد من النوع نفسه، لكنهم مختلفون وراثيًا، تتلف بتفاعلٍ مناعي خاص. تبدأ عملية الإتلاف هذه بظهور مستضدات ملاءمة الأنسجة على سطح خلايا المتبرع مما يثير تفاعلا من قبل جهاز المناعة لدى المتلقي. وبالرغم من أن التناسل الناجح عملية أساسية لكنه يعتقد بأنه يعرّض الأنثى إلى تحد هام بالمستضدات. اقترحت فرضيات متعددة لتفسير بقاء محصول الحمل شبه المغاير حيًّا، على الرغم من تجاهل النتائج المناعية للجماع في كثير من الأحيان. إن الدور المحتمل للبلازما المنوية الكابت للمناعة في التناسل الطبيعي له أهمية سريرية قصوى. وقد يكون غياب هذا الدور في أساليب الإخصاب داخل الأنبوب للتناسل الآدمي سببًا - إلى حد ما - في حدوث معدلات الفشل المرتفعة في هذا الشكل من التناسل المساعَد. إن وجوده في القذف الطبيعي قد يفسر سبب إصابة القناة التناسلية لدى الأنثى بالأورام الخبيثة المحرّضة فيروسيا ويكون عاملا هامًّا يوضح سبب الاصابة بمتلازمة عوز المناعة المكتسب.

It is well recognized that cells or tissues exchanged between genetically dissimilar members of the same species will be destroyed by a specific immune response. This process of destruction is initiated by the expression of histocompatibility antigens on the surface of the donor cells which provoke a reaction by the immune system of the recipient. Successful reproduction even through a fundamental process is thought to expose the female to significant antigenic challenge. Numerous hypotheses have been proposed to account for the survival of the semi-allogeneic conceptus, although the immunological consequences of coitus are frequently ignored. The possible immunosuppressive role of seminal plasma in normal reproduction is clearly of great clinical importance. Its exclusion from the *in vitro* fertilization techniques of human reproduction may partially account for the high failure rates associated with this form of assisted reproduction. Its presence in the normal ejaculate may explain the vulnerability of the female reproductive tract to virally inducted neoplasms and be a relevant factor in the etiology of the acquired immune deficiency syndrome.

Successful reproduction involving internal fertilization and intrauterine gestation is thought to expose the female to significant antigenic challenge. The classic immune response results in the neutralization, elimination, rejection, or destruction of the antigen. Yet such antigenic challenges as do occur following sexual intercourse and during continuing gestation do not usually elicit any immune response harmful to either mother or conceptus. Numerous hypotheses have been proposed to account for the survival of the semi-allogeneic conceptus, although the immunological consequences of coitus are frequently ignored. There is now, however, substantial clinical and experimental evidence to suggest that reproductive performance is enhanced by, and occasionally dependent upon, parental histo-incompatibility.

Since immune responses are generated in lymphoid tissues, many investigators have examined these tissues after mating and during pregnancy. Numerous changes have been reported in different lymphoid tissues, but no consistent pattern of change has emerged. Some of these apparently contradictory observations may have been caused by species differences or strain differences within the species. In addition, the necessary events of reproduction: ovulation, insemination, implantation, and placentation, are associated with well established

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From the Department of Human & Clinical Anatomy (Dr Habbal), Sultan Qaboos University, College of Medicine, Muscat, Sultanate of Oman, and Department of Cell & Structural Biology (Dr. McLean), University of Manchester Medical School, United Kingdom.

Address reprint requests and correspondence to Dr. Habbal: Sultan Qaboos University, Department of Human & Clinical Anatomy, College of Medicine, P.O. Box 32485, Al-Khod, Muscat, Sultanate of Oman.

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changes in the female endocrine system. These changes affect steroid hormone production and these hormones are particularly known to have a profound effect on lymphocytes and lymphoid tissues. The ovarian cycle is controlled by the hypothalamic-pituitary axis through the release of pituitary gonadotropins. The resulting cyclic production of ovarian hormones prepares the female reproductive tract for mating and/or conception. In the event of conception, the normal ovarian cycle is interrupted and pregnancy is initially sustained by hormones from the persisting corpus luteum. At a later stage of pregnancy, the luteal endocrine function is taken over by the placenta.

Immunological Aspects of Coitus

The biological events of reproduction have to be accommodated by the immune system if their outcome is to be successful. The compromising immune system interacts and somehow adapts to the products of conception. Some of the interacting factors are discussed in this review.

The Ejaculate

There now remains little doubt that the immunological component of reproductive function begins with the first coital act and not with the first established pregnancy [1]. There is considerable evidence to suggest that spermatozoa possess surface alloantigens while secretions from the prostate gland and other parts of the male reproductive tract probably constitute another antigen system [2]. In the human, insemination and pregnancy are frequent occurrences and cellular immunity as well as the generation of antibodies against sperm surface antigens and protein constituents of seminal plasma have to be temporarily inactivated and avoided so that conception can succeed.

The antigenicity of spermatozoa is now well established and Erickson [3], reviewing the subject, classified spermatozoal alloantigens as: histocompatibility antigens, male specific antigen (H-Y), blood group antigens (ABO) and differentiation antigens.

A humoral response to spermatozoal alloantigens has frequently been demonstrated [4] and the presence of anti-spermatozoal immunoglobulins in the male is often associated with sterility[5]. High titers of such antibodies have been observed in vasectomized males [6] and after experimentally induced orchitis [7]. In the female, spermatozoal antibodies are not produced following coitus but can be readily induced after administration of spermatozoa by an abnormal route [8].

Seminal fluid comprises approximately 80-90% of the volume of the normal ejaculate. Certain components of seminal fluid are thought to assist the process of fertilization; constituent enzymes facilitate spermatozoal transport through the female reproductive tract and are essential for ovum penetration, while fructose provides an effective energy source for spermatozoal motility [9]. In addition, seminal fluid contains a number of immunosuppressive factors which may protect spermatozoa from immunological damage and prevent sensitization of the female to spermatozoal antigens following coitus [10].

Normally, tolerance to self antigens occurs during intrauterine development or during the neonatal period. Since spermatogenesis begins at puberty, alternative mechanisms must operate to ensure that the young adult male does not become sensitized to his own spermatozoal antigens. The morphology of the testis, and in particular the tight junctions of the Sertoli cells lining the seminiferous tubules, prevent immunocompetent cells and antibodies from gaining access to the developing spermatozoa. During transit through the epididymis and the vas deferens, spermatozoa become coated with seminal fluid components which render them much less immunogenic [11]. The reduction of spermatozoal immunogenicity by seminal fluid may also suppress other immunological processes in the recipient of the ejaculate and this may have undesirable effects [12].

A number of *in vitro* studies have provided convincing evidence that seminal fluid can interfere directly or indirectly with the function of T-cells and B-cells [13], natural killer (NK) cells [9], macrophages [14], antibody [15], and complement [16]. If these effects occur *in vivo*, the host's immune defense mechanisms against infection and malignancy may be significantly reduced. The only published evidence of the effect of seminal fluid on cell mediated immunity *in vivo* suggests that it limits the duration of an effective cytolytic T-cell response to ejaculated spermatozoa [17]. The suppression of NK cells [18,19] has been attributed to the presence of prostaglandins in semen. The activity has been assigned to 19-OH-prostaglandin E (19-OH PGE) [18].

In its reproductive role, the ejaculate is presented to the intact epithelial surface of the female reproductive tract. The allogeneic spermatozoa have to survive the length of journey through the female reproductive tract and yet be removed by phagocytosis [20]. With the beginning of pregnancy there are significant changes in the maternal steroid hormone levels which are recognized as influencing the host's immune response.

The Zygote

The female gamete at the time of ovulation is enclosed within the zona pellucida. If a spermatozoon enters it, the female gamete completes its second meiotic division and male and female pronuclei form. The morula phase of embryonic development proceeds within the zona pellucida which is ovarian in origin. Recent studies have shown that the zona pellucida possesses specific antigenic characteristics [21], but these do not appear to elicit any immune response in the mother.

The need to protect the early embryo within its maternal environment in the upper female reproductive tract by means of the zona pellucida is evident from studies concerned with major histocompatibility antigen expression during the morula stage of embryonic development. During the last decade, however, the advent of congeneic alloantisera and more recently of monoclonal antibodies, has allowed such studies to demonstrate H-2 antigen expression by the early mouse embryo [22]. A study using monoclonal antibodies and an enzyme-linked immunosorbent assay has shown H-2 antigen expression at the two cell, eight cell, and blastocyst stages of mouse embryo development [23]. These workers, by means of papain removal of H-2 antigen from the blastocyte, were able to demonstrate active synthesis of H-2 antigen by the preimplantation mouse embryo; the regeneration time being approximately three hours.

Since the conceptus expresses paternal alloantigens, any immune response, particularly a cell mediated response, generated by non-fertilizing spermatozoa may become a hazard to the survival of the early embryo. The zona pellucida provides the initial protection but with the formation of the blastocyte and the dissolution of the zona pellucida some other mechanism must operate to safeguard the implanting conceptus from immunological attack.

Mucosal Immunity

When an antigenic challenge is presented to the host at a mucosal surface it is usual for a local immune response to occur. Although not necessarily limited to the lymphoid tissue of that mucosal surface, specific antibody or T-cells are rarely demonstrable in the peripheral circulation. There is now considerable evidence of this form of local immunity occurring at various mucosal surfaces in the gastrointestinal, respiratory, and female reproductive tracts as well as in the salivary and mammary glands [24,25].

To maintain local immunity, repeated antigenic challenge is necessary since there is little evidence to support the concept of immunological memory, at least for the humoral component of mucosal immunity [26]. Evidence that IgA is produced in mucosal associated lymphoid tissue is provided by the observation that lethally irradiated rabbits, reconstituted with cells from Peyer's patches or bronchial lymphatic tissue, become repopulated with IgA-containing cells [27]. In a review of mucosal immunity [26], it was suggested that mucosal associated lymphoid tissue (MALT) forms its own partially isolated system with its own specific lymphocytes. Indeed many B-cells from the thoracic duct, on reintroduction into the blood, home to the gut associated lymphoid tissue (GALT) where they produce IgA [28].

The genital tract in most female mammals provides a direct pathway from the external environment into the peritoneal cavity. The presence of subepithelial lymph follicles in the vagina, cervix uteri, and uterus and the tendency for IgA-containing cells to localize [26] , is clearly of significance as a defense mechanism against infection, as well as being important in any consideration of the immunological effects of reproduction. The appearance of large numbers of lymphocytes in the vagina of the rat during diestrus and the accumulation of IgA secreting cells during proestrus [29] may indicate that ovarian hormones control the capacity of the female's reproductive tract to respond to antigenic challenge. In addition to the substantial evidence available for B-cell participation in mucosal immunity, the various subsets of T-cells have been identified in mucosal associated lymphoid tissues [26,30]. This mucosal T-cell population increases in response to local challenge and diminishes with its removal [31]. Lymphocytes reach mucosal associated lymphoid tissue from the blood and leave directly into the lumen or via efferent lymphatics. These lymphatic vessels form a rich plexus in the female reproductive tract and in the rat and rabbit drain primarily to the internal iliac and para-aortic lymph nodes [32]. Although the female reproductive tract is generously endowed with lymphatic vessels, the endometria of the rabbit [32], mouse, and rat [33] seem to be devoid of lymphatics. The absence of endometrial lymphatics has been suggested as an explanation for the prolonged survival of endometrial skin grafts in the rat [34] and rabbit [35]. Although it is normally assumed that local antigenic challenge at a mucosal surface excites no systemic response, such a response has been demonstrated after artificial insemination of allogeneic epididymal spermatozoa [36] and after normal mating [37].

Immune Response to Mating

Spermatozoa within the upper female reproductive tract retain their ability to fertilize for varying periods according to the species. In common laboratory animals, this period is approximately 6-36 h [38], but in man it may be as long as five days (McLean JM, in press).

Non-fertilizing spermatozoa are removed from the uterine cavity and tubes of the mouse and rat within 24 h of mating despite the continued presence of the copulatory plug [39]. This removal of spermatozoa is effected mainly by the action of polymorphonuclear leukocytes and mononuclear macrophages [39-41]. The maternal postcoital leucocytosis evident in the female reproductive tract is probably induced by chemotactic mechanisms [40] and may be hormonally controlled [42]. Some spermatozoa penetrate the uterine mucous membrane and large numbers of spermatozoa invade the endometrial glands [43]. Such penetration of the uterine epithelium may result in transfer of genetic material with the possible risk of neoplasia [44]. That this poses a potential risk is suggested by the observation that spermatozoal nuclei may induce DNA synthesis in somatic cells [45].

Almost 30 years ago, it was shown that radiolabeled epididymal spermatozoa injected into the uterine lumen were found 17 h later in the endometrium, pelvic lymph nodes, and spleen [46]. More recently, radiolabeled allogeneic epididymal spermatozoa were introduced into the uterine cavity of the rat by artificial insemination during the estrous phase of the ovarian cycle [47]. This study demonstrated that spermatozoa entered the female host within four hours of insemination and reached the various tissues of the lymphoid system being preferentially concentrated in the uterine regional lymph nodes, thymus, and spleen.

Various explanations have been advanced to account for the absence of a coital immune response and include effective phagocytosis of spermatozoa and rapid evacuation of the female reproductive tract [48], presence of blocking antibodies [49], and the immunosuppressive effect of seminal fluid [10,11]. Recent work with rats has shown that subcutaneous and intrauterine challenge with allogeneic epididymal spermatozoa as well as first allogeneic mating generate specific anti-male strain cytolytic T-lymphocytes in the regional lymph nodes of the female recipients. After subcutaneous and intrauterine challenge, the specific cytolytic T-cell response continued until the fifth day, while after first allogeneic mating, was limited to the second and third postcoital days, being no longer detectable at the time of implantation on the fifth postcoital day [17]. This "switch off" of the cytolytic T-cell response to mating during the pre-implantation period suggests that one factor in the seminal fluid exerts a suppressive function on the female host's immune response to spermatozoal alloantigens. A limited cytolytic T-cell response to coitus resulting from the effects of seminal fluid is clearly beneficial in reproduction, but may have adverse effects for the host when exposed to virally infected ejaculate. The seminal fluid's immunosuppressive activity is now well established. Prostaglandins are present in large quantities. PGE 1 & 2 are present in equal amounts in human semen and are immunosuppressive [50]. Prostaglandins may account for all the immunosuppressive activity in semen since seminal plasma that is stripped of its lipids has little, if any, effect. A high molecular weight immunosuppressive factor has been identified as particulate and corresponds to prostasomes [51]. These are small trilamellar and multilamellar vesicles produced by the acinar cells of the human prostate [52] and found in large numbers in semen. Prostasomes have been shown not only to inhibit lymphocyte proliferation but also to inhibit the ability of macrophages to phagocytose latex beads. In addition, prostasomes have been found to bind to sperm [53]. This may represent a method by which immunosuppressive protection is carried by the sperm up the female reproductive tract. They also have an intrinsic enzyme activity which is thought to mediate their adhesive properties rather than their ability to inhibit mitogen-induced lymphocyte proliferation. Seminal prostaglandins may have a direct effect on sperm metabolism and may be associated with alteration of sperm function [54]. In fact, it has been reported that infertile men have significantly lower levels of prostaglandins in their semen. Both fertile and infertile human semen contain varying numbers of leukocytes including neutrophils [55]. Interaction between seminal prostaglandins and leukocytes is present in human semen. Neutrophils and other phagocytosing cells may produce cytotoxic agents which may be detrimental to sperm movement [56]. They are responsible for poor performance in the zona-free hamster egg penetration assay [57]. Prostaglandins can suppress both neutrophils and macrophage function and may therefore have a beneficial effect on sperm motility [58], their performance in the zona-free hamster egg penetration test, and on fertility.

There can be little doubt that prostaglandins and prostasomes are powerful immunosuppressive agents in human semen and when introduced in the female may have an effect on the immune system. This is clearly demonstrated when semen is introduced into an abnormal route. Anal deposition of semen can lead to depression of the whole body's immune system as was shown in rabbits [59] and rats [60]. This is particularly relevant to the pathogenesis of Acquired Immune Deficiency Syndrome (AIDS) found in homosexual males since the host's defense against viral infection is predominantly a cell mediated response and there is now a well established etiological link between human papilloma viral infection and cervical neoplasia [61].

Lymphoid Tissue Response to Coitus

Some active immune response by the female during pregnancy is important, if not essential, to successful reproduction [62]. Since immune responses are generated in lymphoid tissues, examination of these tissues in female animals after mating is an appropriate means of investigating any postcoital response. Lymphoid tissues are, however, also responsive to steroid hormones and many of the initial studies of lymphoid tissues after mating were unable to determine the influence of the consequential changes in steroid hormone levels.

Although antigenic challenge is not associated with recognized changes in the primary lymphoid organs, certain changes do occur in secondary lymphoid tissues. Exposure of a host to alloantigens is followed by well documented changes in the regional lymph nodes which increase in size and demonstrate lymphocytic proliferation in their paracortical zones, as well as lymphocytic accumulation [63]. These changes are associated with the simultaneous generation of specifically activated T-cells and B-cells [64]. Comparable changes occur in the spleen following antigenic challenge [65].

Observations on the thymic response during pregnancy have been concerned with the effects of steroid hormones. The response of the thymus during pregnancy is generally considered to be one of involution. In the mouse, observations are of continuous involution from the onset of pregnancy [66] or of involution beginning later during gestation [67]. In the rat, this variability in the onset of thymic involution during pregnancy has been shown to be strain-dependent [68] and this presumably explains the conflicting results found in mice. The adrenocortical steroids, which are closely related to the gonadal steroids, also induce thymic involution [69]. Indeed it has been known for some time that adrenalectomy is followed by thymic enlargement [70]. Thymic weight has been found to be significantly different during allogeneic and syngeneic gestation around mid-term [67,71]. Another presumptive immunological effect on the gestational thymus was the observation that involution in mice could be prevented by prior sensitization with paternal skin [72]. An immunological effect on the gestational thymus has also been observed in the rat; allogeneic pregnancy being associated with an increased level of lymphocyte proliferation [68]. The thymic changes associated with pregnancy are presumably the result of hormonal changes as well as the presence of an allogeneic conceptus, although it is interesting to note that the circulating levels of various thymic hormones remain constant during pregnancy [73].

The uterine regional lymph nodes are situated around the bifurcation of the great vessels at the pelvic brim and along the course of the internal iliac artery on the side wall of the pelvis. During pregnancy their weight increases and most reports suggest that this increase is greater during allogeneic pregnancy than syngeneic pregnancy [1,36,67,71,74-76]. Observations at five day intervals throughout pregnancy [77] have not shown the uterine nodes to be consistently heavier during allogeneic than syngeneic pregnancy and it is now evident that the gestational uterine regional lymph node weight response is strain-dependent. Lymph node weight reflects cell content but gives no indication of in situ cellular proliferation which is an important sign of an immune response. Histological examination has revealed an increase in the number of large pyroninophilic cells and plasma cells in the uterine regional lymph nodes during rat pregnancy [78]. These observations were confirmed [37] and showed a significant increase in large pyroninophilic cell counts, which persisted until the sixth day and were significantly greater during allogeneic than syngeneic pregnancy. This unequivocal histologic evidence of a cell mediated immune response to allogeneic mating and pregnancy was accompanied by comparable evidence of a humoral response.

Reports of peripheral lymph node changes during pregnancy have generally been unremarkable. However, Forster et al [71] did notice a significant increase in the proportion of proliferating cells in popliteal lymph node smears at ten days of allogeneic pregnancy when compared with the same stage of syngeneic pregnancy or virgin controls. This popliteal proliferative response during allogeneic pregnancy was shown by Shaya et al [1] to begin before implantation while the comparable histological study [37] demonstrated the pattern of large pyroninophilic cell response in the popliteal nodes during the first ten days of allogeneic pregnancy to be identical with that in the uterine regional lymph nodes. Such evidence suggests that antigens in the female reproductive tract reach the lymph nodes via the blood as well as by lymphatics. Indeed the blood may be the principal means of access since the regional node response could be due to blood borne antigen while that in the distal popliteal nodes could not be due to antigen access by afferent lymphatics.

Splenic weight gain was reported in the mouse and rat. These results suggest gestational splenomegaly with varying significant responses during syngeneic and allogeneic pregnancies [67,71,74,75,77,79]. It is apparent from these results that tissue weights provide inadequate data to assess the immunological function of the spleen during pregnancy, probably because of gestational changes in its hemopoietic function [65]. A significant increase in the lymphocyte content of the rat spleen during allogeneic pregnancy was reported by McLean et al [74], but this was not confirmed by Forster et al [71]. However, both groups of workers observed a significant increase in the percentage of proliferating lymphocytes in the spleen during allogeneic pregnancy. Nevertheless, it is generally thought that the mitogenic response of rat and mouse spleen cells to a number of specific and nonspecific stimulants is depressed during pregnancy [80]. The functional significance of this depression of mitogenic activity during pregnancy remains unknown. It is generally believed that the splenic response during pregnancy is non-immunological [81], although the evidence for this view is equivocal. Nevertheless, it must be accepted that there is insufficient consistent data from splenic observation during pregnancy to identify its exact role in the immunological events of reproduction.

Since blood is an important vehicle for lymphocyte transport, it was assumed that assays of the various lymphocyte subsets in peripheral blood during pregnancy might yield useful information. Unfortunately, this has not been so, perhaps because the major effects of any immune response occur within the lymphoid tissues. Certainly during human pregnancy no consistent change in peripheral blood lymphocyte subsets has been observed [48]. The total blood lymphocyte count increases during the latter part of pregnancy in women [81] and also in rats. Observations during rat pregnancy indicate that the increase begins prior to mid-gestation [79] and is more marked during allogeneic than syngeneic pregnancy [82].

Conclusion

It is only recently that the significance of the immunosuppressive role of the male ejaculate has been elucidated. The clinical implications are far reaching when applied to organ transplantation [83]. Sexually transmitted diseases may owe their establishment in large part to the depression of humoral and cell mediated immunity provided by the semen vector. The localized and temporary immunosuppression caused by prostaglandins in semen may be sufficient to facilitate viral infection such as HIV. Prostaglandins increase the HIV replication rate. This is also true for infection with other viruses such as herpes, cytomegalovirus (CMV) and human papilloma virus (HPV). A sexually active woman with repeated exposure to these immunosuppressive agents may have her normal immuno-surveillance mechanisms as operated by NK cells and cytotoxic T-cells either nonfunctioning or impaired sufficiently for the change of pre-cancerous into cancerous cells. By implication, semen deposition may play a crucial role in the etiology of cancer of the cervix as well as facilitating its initial infection [44].

The contribution of the immunosuppressive substances in seminal plasma to the spread of sexually transmitted diseases may be seriously underestimated. Viruses such as type-2 herpes, CMV, and hepatitis-B may exist as unrecognized subclinical infection in the male reproductive tract.

The prostate is the reservoir for prostasomes and its ability to deliver such a potent immunosuppressive agent in the ejaculate may lead to pathology of the male reproductive tract. It is possible that the male's own immune surveillance may become depressed with prostatic carcinoma as the end result. Immunosuppression in semen is crucial for successful reproduction. But the price paid today in terms of reproductive pathology due to organisms exploiting the weaknesses imposed on the female immune defenses is indeed high. More optimistically for the future, organ transplantation may find in prostasomes an alternative immunosuppressive agent that is free from the unpleasant side-effects of steroids and cyclosporins. Furthermore, elucidation of the immune mechanisms involved in the adaptation of the immune system of the semi-allogeneic conceptus may indeed revolutionize the protocols of organ transplantation. The recent advances in this field and the far reaching implications indicate that this goal may not be too far in the future. •

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Case Reports

FOCAL SEIZURES, A MANIFESTATION OF STROKE IN AN UNSTRESSED FULL TERM NEONATE

Poonam Singh, MD; Balbir Singh, MD; Masood Khan, MD

Focal cerebral infarction remains an uncommon diagnosis in full term unstressed babies despite advancement in radiological techniques. However, it is not rare in autopsy series. In 1979 Barmada et al [1] reported a 5.4% incidence of focal cerebral infarction acquired perinatally in full term neonates in an autopsy series. Review of current literature thus far has revealed around 35 full term babies with focal infarctions, mostly in the territory of the left middle cerebral artery. Most of these babies have experienced significant perinatal asphyxia. Thus far, only seven babies, unstressed and apparently normal with good Apgar scores, have developed focal cerebral infarction. PLEDS has not been reported in any of these babies. Prognosis of these babies, including ours, has been better as compared to those who suffered perinatal asphyxia [2].

Case Report

A full term female baby was delivered at Riyadh Armed Forces Hospital (RKH) to a 24-year-old gravida 4, para 3, whose pregnancy was uncomplicated. The baby's birth weight was 3.3 kg, OFC 34.5 cm, and Apgars were 9 and 10 at one and five minutes. No active resuscitation was required. The placenta looked grossly normal and weighed 600 gm. At 18 h of age, clonic movements of the right half of the body were noted which lasted for approximately one-half h. These seizures recurred four times within the ensuing 24 h. Physical examination revealed a baby in no apparent distress, pink on room air, who was well perfused. Fontanelles were normal. Pupils were equal and reactive. Doll's eye movements were normal. Tone was normal and equal in all extremities. Deep tendon reflexes (DTRs) were symmetrical. The infant had a symmetrical Moro reflex. Examination of the cardiovascular system did not reveal any murmurs. Laboratory investigations revealed hematocrit of 0.47. Septic screen including lumbar puncture was normal. Glucose was 4.5 mmol/L, calcium 2.24 mmol/L, and magnesium 0.72 mmol/L. Coagulation screen was normal. Protein C and S were normal. Electrocardiogram was normal for age. Echocardiogram was normal. Cranial ultrasound did not reveal any bleeds. Ventricle size was normal. There was no evidence of cerebral edema or focal lesions. Computerized tomographic (CT) scan performed at the age of five days revealed an area of low attenuation in the left parietal region (Figure 1). There was no mass effect. The lesion was suggestive of infarction in the distribution of left middle cerebral

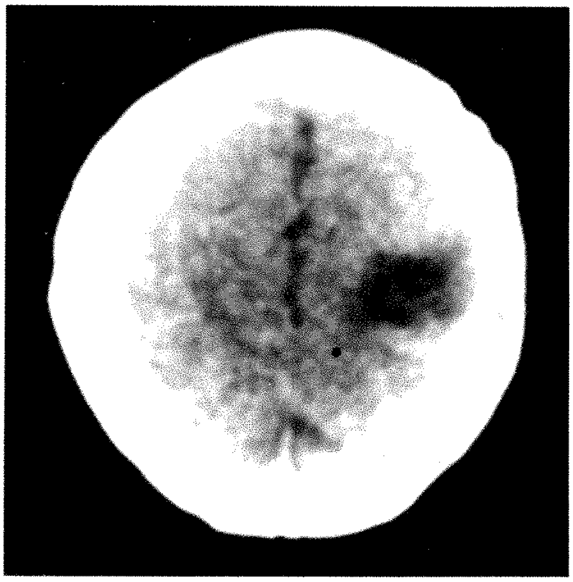

FIGURE 1. CT scan of head showing area of low attenuation in left parietal region.

From the Department of Neonatal Intensive Care (Drs. P. Singh and Khan) and the Department of Pediatrics (Dr. B. Singh), Riyadh Armed Forces Hospital, Riyadh.

Address reprint requests and correspondence to Dr. P. Singh: Riyadh Armed Forces Hospital, Department of Pediatrics, P.O. Box 7897, Riyadh 11159, Saudi Arabia.

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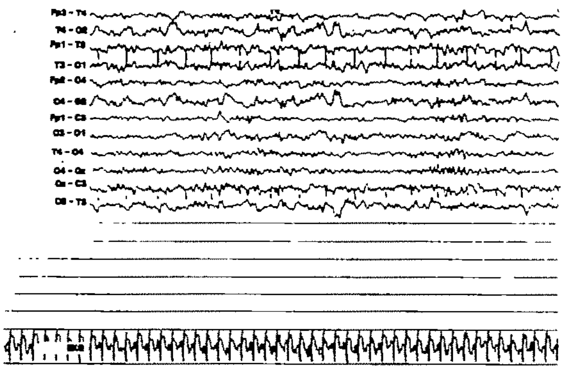

FIGURE 2. EEG showing left sided periodic epileptiform discharge (PLEDS).

artery. Electroencephalogram revealed periodic lateralizing epileptiform discharges arising from the left side (Figure 2). The baby was loaded with phenobarbitone 20 mg/kg. She also required additional doses of diazepam 0.3 mg/kg within the first 24 h. The seizures did not recur after the first day. There was no sign of focal neurological deficit. She was gradually taken off the anticonvulsant without recurrence of symptoms. The baby has been seen in the follow-up clinic on several occasions. She has no neurological deficit or recurrence of seizures. Her development, including speech and language, is normal at 1-1/2 years of age.

Discussion

Cerebral arterial infarction was the second most common cause in a series of 54 full term babies with seizures, second only to hypoxic ischemic encephalopathy [3]. Etiology and pathogenesis of stroke in the neonate has been largely speculative. Implicating factors include embolization from placenta or villus thrombus, patent ductus arteriosus, cyanotic heart disease, twin-to-twin transfusion, and catheterized vessels; thrombosis secondary to traumatic vascular damage, disseminated intravascular coagulation, protein C and S, anti-III deficiency, polycythemia, meningitis, sepsis, and now becoming increasingly common, cocaine drug abuse [4]. The territory of the left middle cerebral artery is affected 50% of the time.

Obstetric history is suggestive of perinatal asphyxia in most case reports except the seven "idiopathic" infarcts and in ours in which there were no risk factors. Seizures may be focal, clonic, multifocal, or subtle, and usually have their onset at 8-60 h of age. Physical examination was normal in most patients. Some asymmetry of tone may be noted.

The study of choice in full term babies with focal seizures is CT of the head performed within 2-14 days following insult. This usually reveals a wedge-shaped area of decreased attenuation with irregular boundaries. By 4-10 days, the infarct has increased to maximum size and may show a mass effect. By 3-4 weeks, cavity formation begins. Four infants with strokes *in utero* have been reported. This was proved by well defined porencephalic cysts by day eight without evidence of cerebral edema. One patient was diagnosed on antenatal ultrasound [5].

Most authors have reported multifocal abnormalities on EEG. PLEDS, although a well known marker of stroke in adults, has only been infrequently reported in neonates with stroke [6,8]. PLEDS lacks specificity as it may be seen in neonatal herpes, structural and metabolic abnormalities [6,7].

No long term follow-up series are available due to the relatively recent recognition of the problem. The general prognosis is good for term babies with focal brain insults occurring perinatally with 62% having no neurological sequelae. Thirty-one percent were left with motor deficits, mainly hemiparesis. Seizures remained a common disability, occurring in 24% of survivors. Seizures may occur after a latent period of 2-3 years. This is important to recognize. Clinically silent neonatal stroke may be a cause of focal epilepsy occurring later in childhood. Subtle learning disabilities, attention deficit disorders, and cognitive disturbances later in life may also arise from perinatal stroke. The outcome differs significantly in preterm babies or full term babies with multifocal infarctions.

In conclusion, unifocal cerebral infarction is a relatively common cause of seizures in full term babies. This condition is best diagnosed by a CT scan. With better recognition of the pathophysiology of vascular occlusion following asphyxia, it may be possible to prevent additional damage by anticoagulation or prostaglandin inhibitors. On short term follow-up, the neurological outcome appears to be good in babies with "idiopathic" cerebral infarction. PLEDS may be an additional diagnostic marker for focal infarction in neonates.

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TREATMENT OF BILATERAL TUBAL ECTOPIC PREGNANCY BY CONSERVATIVE TUBAL SURGERY

Jacob A. Unuigbe, MRCOG, FWACS, FICS; Farag S. Shaheen, DGO, DS, MRCOG;
Muharram H. Hassonah, DGO, MRCOG; Afaf Hassa Abdulla, MD, D.Path

Several reports on multiple ectopic pregnancy have inundated medical journals during the last two decades, including two recent case reports from the Middle East [1,2], each addressing combined extrauterine and intrauterine pregnancy. Many of these are associated with induction of ovulation. This case report, in addition to adding to the number of reported cases, is presented because of the peculiarity of clinical presentation and the successful conservative surgical treatment of bilateral tubal pregnancy encountered at laparotomy.

Case Report

A 23-year-old Saudi female, para 1 + 0, had a cesarean section delivery two years prior to presentation. She was admitted with acute abdominal pain associated with vomiting and dysuria the night of 23 January 1992. She had seven weeks of amenorrhea with a positive report on pregnancy test conducted on an early morning specimen of urine one week prior to admission. There was no history of infertility investigation or induction of ovulation. On clinical assessment, her vital signs were stable. Examination revealed a scaphoid abdomen with marked tenderness confined to the suprapubic, iliac, and lumbar regions. No masses were palpable and there was no evidence of fluid collection. On pelvic examination, there was brown vaginal discharge. The cervix was long with a closed os and there was minimal cervical excitation pain. The uterus was slightly bulky and no adnexal masses were palpable. A diagnosis of severe urinary tract infection in early pregnancy was made. The possibility of an ectopic pregnancy was, however, entertained. Immediate microscopy on a midstream specimen of urine yielded 10-15 WBCs per high power field with a bacterial colony count greater than 10^5/ml, and subsequent culture grew E. coli. She made remarkable clinical progress overnight while on intravenous fluid and antibiotic therapy. Ultrasonic abdominal and transvaginal pelvic scan conducted in the morning revealed a slightly bulky uterus with thickened endometrium containing some blood streaks but no fetal echos in the cavity. There was evidence of an echogenic mass 5.5 x 3.5 cm situated in the pouch of Douglas, more to the right side, with some fluid collection. Both ovaries were visualized and separate from the mass. The findings were suggestive of a right tubal ectopic gestation.

On the strength of the ultrasound findings, arrangements were made for emergency exploratory laparotomy. Laparotomy was performed by excision of a wide, poorly healed, subumbilical midline keloid scar tissue.

The findings at laparotomy were as follows: the uterus was within normal limits in size with no evidence of pregnancy. There was a dark brown swelling of the ampulla of the left fallopian tube, measuring about 2 cm in diameter and 3 cm in length close to the fimbria with some trickling of blood through the fimbrial ostium into the peritoneal cavity. The right ampulla contained three beaded swellings, the largest at the fimbrial end measuring about 2 cm in diameter. There was also some trickling of blood through the right fimbrial ostium. Both tubal swellings showed no evidence of rupture. The left ovary was polycystic and slightly enlarged. There was about 100 ml of blood with several small clots in the pouch of Douglas.

As both tubes were pathologically affected, further surgical procedures to conserve them were

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From the Department of Obstetrics and Gynecology (Drs. Unuigbe, Shaheen, Hassonah), and the Department of Pathology (Dr. Abdulla), Prince Salman Bin Abdulaziz Hospital, Riyadh.

Address reprint requests and correspondence to Dr. Unuigbe: Prince Salman Bin Abdulaziz Hospital, P.O. Box 56773, Riyadh 11564, Saudi Arabia.

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embarked upon. The contents of the right tubal swelling (blood clots, some tissue, and a small gestational sac) were easily expressed through the fimbrial ostium. As it was impossible to express the contents of the larger left tubal swelling, a left salpingotomy was performed. A small linear longitudinal incision was made over the superior convexity of the tubal swelling and the products of conception with blood clots were evacuated with forceps. The incision was closed with interrupted #3-0 chromic catgut. The pelvic cavity was rinsed with normal saline and a Redi-Vac drain was left in the pouch of Douglas.

The patient had an uncomplicated recovery and was discharged home on the seventh postoperative day. Pregnancy test on early morning specimen of urine collected on the sixth postoperative day was negative and serial serum beta HCG levels two and four weeks following surgery were undetectable. The patient had normal menstruation a week following discharge from the hospital. Histopathology of the separate specimens from the right and left fallopian tubes revealed organized blood clots containing both syncytial and Langerhans' cells of chorionic villi and syncytial large giant cells, thus confirming the diagnosis of ectopic pregnancy in each tube (Figures 1 and 2). Hysterosalpingogram performed six weeks following surgery confirmed patency of both fallopian tubes with prompt peritoneal spill of the medium into the peritoneal cavity.

Discussion

Records in the literature abound with cases of multiple ectopic pregnancies, a majority of which are combinations of intrauterine and extrauterine gestations [1-4]. Reports are, however, scarce on bilateral tubal pregnancy [5], and indeed, Howkins and Hudson [6] emphasized the rarity of this variety, believing that some of the reported cases of bilateral tubal ectopic pregnancy that have crept into the literature may well have been hematosalpinges in the tubes unaffected by ectopic gestation. Confirmation of the diagnosis lies with histologically proven presence of chorionic tissue in the products evacuated from each tube.

It is interesting to note that this patient did not use ovulation induction drugs, which account for many recently reported cases. Multiple extrauterine

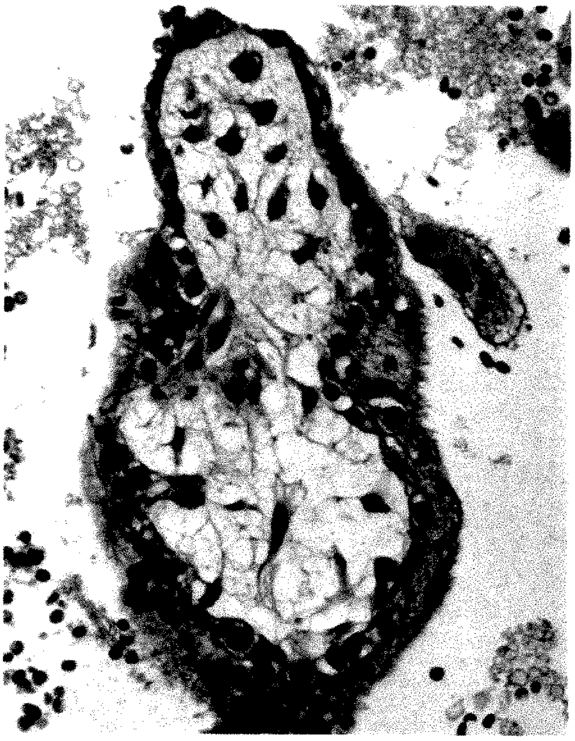

FIGURE 1. Histology of specimen from left fallopian tube. Chorionic villi with synctial and Langerhans' cells. Hematoxylin and eosin (200x).

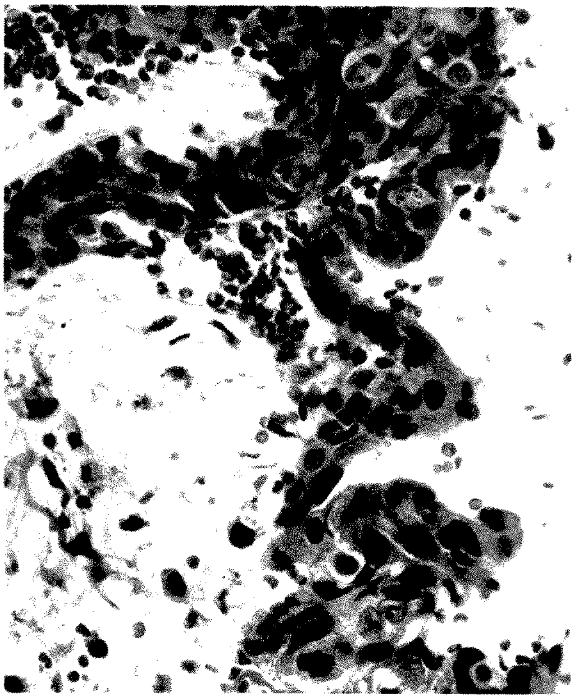

FIGURE 2. Histology of specimen from right fallopian tube, trophoblastic (syncytial and Langerhans') cells, hematoxylin and eosin (200x).

pregnancies, like multiple intrauterine pregnancies, continue to increase in incidence with use of these drugs [2]. This calls for increased vigilance in the management of patients with features of ectopic pregnancy. Not only is the exclusion of intrauterine pregnancy important preoperatively, but careful inspection of both tubes and ovaries and the pouch of Douglas at subsequent laparotomy is mandatory.

Conservative treatment becomes an important consideration with increasing incidence of multiple, notably bilateral, tubal ectopic pregnancy. Conservative surgical treatment is indicated where, at laparotomy, such pathology as described in this report is encountered, especially in young women of low parity or those undergoing investigations for infertility. Clearly, radical surgery is contraindicated, especially when no rupture has occurred. Various conservative surgical methods have been employed: expression of the products of conception from the tube as previously described, the so-called "terminal milk-out" or "squeeze-out" procedure [7]; linear salpingotomy described by Stromme in 1953 and 1973 [8,9]; and salpingostomy, either at laparotomy or through laparoscopic route [10,11]. Microsurgical techniques, when available, greatly improve the outcome of these procedures.

When an unruptured ectopic tubal pregnancy is detected (as is frequently the case with increasing application of transvaginal sonography to detect early pregnancy complications), a case has been made for use of non-surgical conservative treatment with cytotoxic chemotherapy. Tanaka et al [12] and recently Altaras et al [13], reported on the successful use of methotrexate and Actinomycin D, respectively, in the treatment of interstitial ectopic pregnancy. They warn, however, of undesirable side effects and possible increased incidence of congenital fetal anomalies following cytotoxic therapy. Ory [14], in a recent review, while recognizing the safety and effectiveness of methotrexate, recommends its application for those lacking the capability to provide laparoscopic surgical treatment and for physicians and patients who have a preference for non-surgical treatment. In addition, cytotoxic chemotherapy, notably methotrexate, is the treatment of choice for persistent trophoblastic disease which may complicate ectopic gestation. Chemotherapy may be used as an adjunct to conservative surgery in patients with persistent ectopic pregnancy [10,11,15] who display evidence of persistent trophoblastic activity (high levels of urinary or serum beta HCG or positive pregnancy test on dilute urine specimens) postoperatively.

While it is recognized that tubal function is not only determined by patency, it is important in predicting the reproductive future of the patient to confirm tubal patency by performing a follow-up hysterosalpingogram or laparoscopic dye test. Tubal patency following conservative tubal surgery as demonstrated by hysterosalpingogram is of the order of 65-100% in the reported series [10,11]. Even with proven tubal patency, the patient needs careful monitoring as the potentials for recurrence of ectopic pregnancy remain high [10], particularly with the evident sacculations of the right tube reminiscent of chronic pelvic inflammatory disease, salpingitis isthmica nodosa, or complicated localized diverticula of the ampulla, all pathological conditions etiologically associated with ectopic tubal pregnancy [16,17].

Proven urinary tract infection coincided with and temporarily masked the clinical picture of ectopic pregnancy in the case reported. With such atypical clinical presentation, ultrasonic scan (notably transvaginal imaging and the Doppler technique), is of immeasurable value [18,19]. The important lesson here is that the presence of other pathology does not exclude ectopic pregnancy.

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MACRODACTALY OF BOTH HANDS AND FOOT ASSOCIATED WITH CUTANEOUS HEMANGIOMATA: A CASE REPORT WITH REVIEW OF THE LITERATURE

Mona Fouda, MBBS, MRCP(UK); Riad A. Sulimani, FRCR(C), FACP

An unusual case of macrodactaly in a 14-year-old Saudi female is reported. The patient's hands and one foot were involved and she also had cutaneous hemangioma. This is the second case in the literature of combined hands and foot involvement, the first case reported by Kalen et al [3] but which was thought at that time to represent Klippel-Trenaunay syndrome. This is the first report of the combined skeletal deformities with skin lesions.

Macrodactyly, as the name implies, is enlargement of the digits of the hands and feet. True macrodactyly has been a known entity since 1967 when Barsky [2] published the first literature review on the condition which included 72 cases. Since then, additional cases have been added with classification of the anomaly into various types including the static variety, progressive variety, isolated macrodactyly, and macrodactyly associated with other syndromes.

Up to 1988, nearly 180 cases have been reported in the world literature with one case in the Kalen et al series of combined deformity in both hands and one foot [3]. Ours is the second of such a combination and probably the first in association with cutaneous hemangiomata.

Case Report

A 14-year-old Saudi female from the northern region of Saudi Arabia presented to the endocrinology clinic of King Khalid University Hospital (KKUH) with a history of having long deformed fingers and toes since birth which became progressively larger with age and were now causing joint pains mainly in the hands. The patient noted a small swelling of long duration under the skin of the anterior chest wall and during the past year, a similar tender swelling appeared on the right hand along the radial aspect of the thumb. The patient is the middle child of four girls and two boys, all of whom are normal. The parents are first degree cousins, but neither family has such an anomaly in any member.

On examination, the patient was a tall, thin girl. Her weight was 36.5 kg and height 147 cm. She had normal facies and normal body habitus. The right hand demonstrated bulky lateral deviated index and middle fingers with hyperflexible joints. There was a firm to hard nodule subcutaneously along the radial side of the thumb which was tender and slightly mobile. The left hand also had long and bulky laterally deviated index and middle fingers; the ring and little fingers were longer and larger than her normal fingers (Figure 1). The appearance of the left foot is noted in Figure 2 and demonstrates the third, fourth, and fifth toes to be larger and longer than the

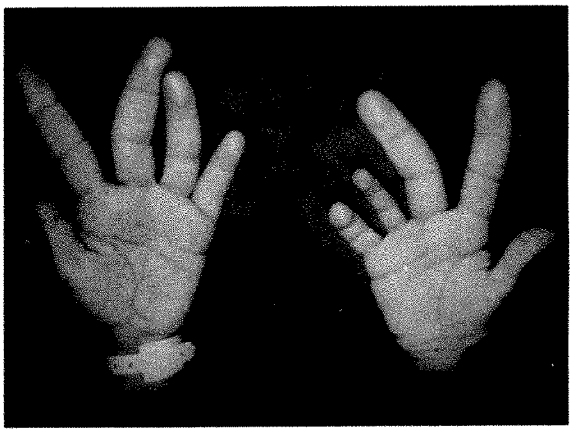

FIGURE 1. Shows the enlarged laterally deviated index and middle fingers of the right hand as well as the small nodule at the base of the thumb. It also shows the enlarged deviated index and middle fingers of the left hand and also that the ring and little fingers are larger on the left hand than on the right hand.

From the Department of Medicine, College of Medicine, King Saud University, Riyadh.

Address reprint requests and correspondence to Dr. Fouda: King Saud University, Department of Medicine (38), College of Medicine, P.O. Box 2925, Riyadh 11461, Saudi Arabia.

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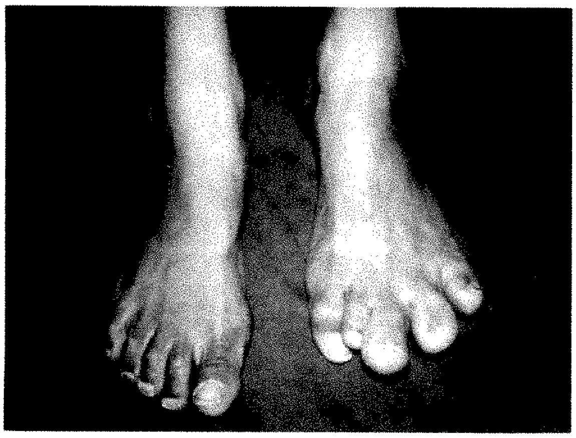
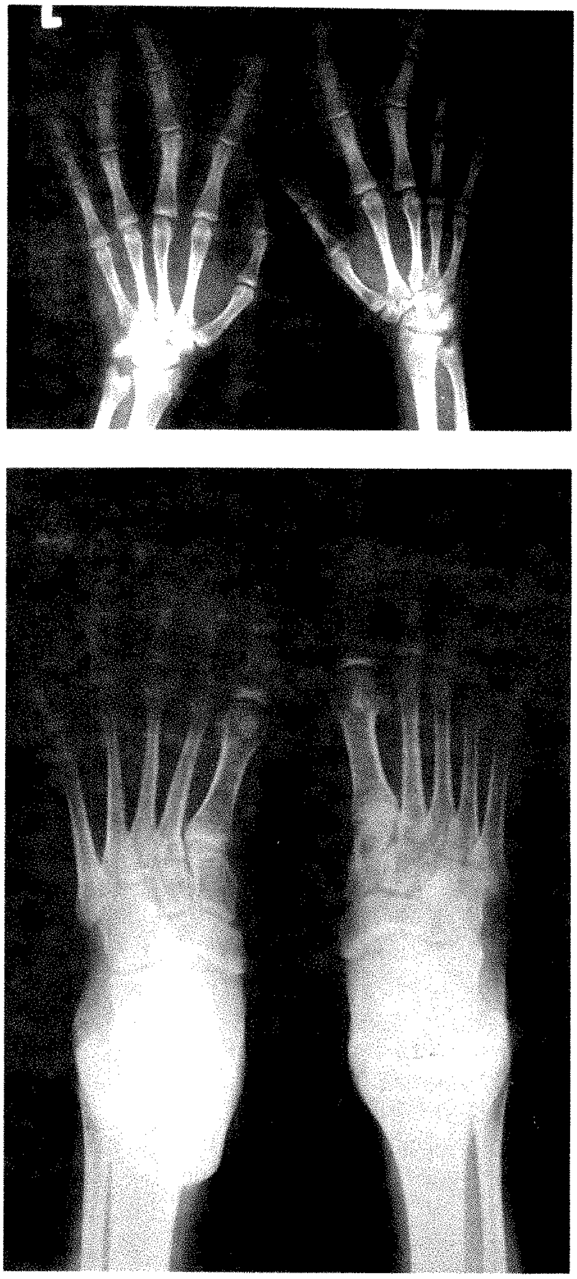


FIGURE 2. Shows enlargement of the third, fourth, and fifth toes on the left foot.

other toes. The right foot appeared to be normal. The remainder of the examination was normal. The investigations showed normal biochemical and hormonal profiles, growth hormone, and somatocedin-C levels.

X-rays of the patient's hands and feet are noted in Figure 3. The lesion on the hand was biopsied to determine whether or not it was a neurofibroma; the histopathology revealed a hemangioma (Figure 4). We believed a similar lesion on the chest to be another hemangioma. Later on the patient underwent surgical correction of the fingers. A wedge osteotomy of the left ring finger with K-wiring and reduction of the macrodactyly of the index finger was performed. Pathology reports showed fibrofatty tissue covered with hyperkeratotic skin. The patient is scheduled to have surgery in a few months for further reduction and osteotomy if needed.



FIGURES 3a & b. Two x-ray photographs of both hands and feet showing the enlarged bones of the same affected digits and the enlargement is of the phalanges as well as the metacarpals/metatarsals.

Discussion

Macrodactyly is a rare skeletal anomaly involving the hands and/or feet. It is usually a sporadic disorder as seen in our patient. True macrodactyly is differentiated into two types; the static variety or macrodactyly simplex congenita in which the enlarged digit is present at birth and does not increase disproportionately with growth, and the second variety, the progressive type or macrodystrophia lipomatosa progressiva, in which there is growth of the involved digit(s) which grow in size at a faster rate than expected from normal growth [1]. True macrodactyly was reported by Barsky [2] to be more common in the hands than in the feet, but in the Kalen et al series (the largest series reported in the Western hemisphere), no such difference was reported [3]. Also, Barsky [2] reported a higher incidence in males than in females while Kalen et al [3] reported an equal sex ratio in the cases involving the hands but significant male predominance in the pedal cases. Bilateral

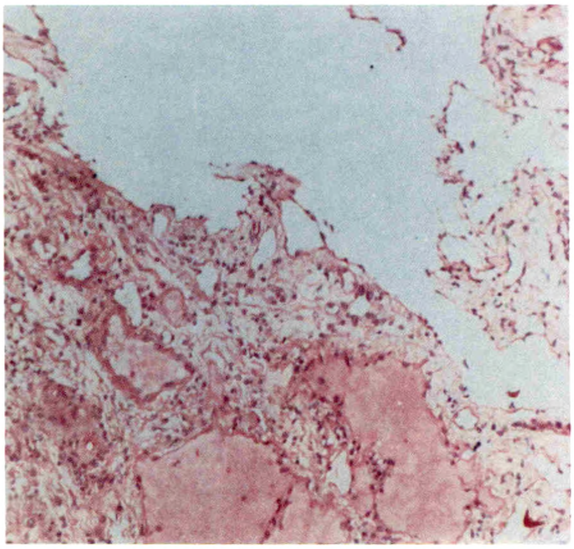


FIGURE 4. A histopathology slide of the nodular lesion at the base of the right thumb excised and shows vascular channels lined by endothelial cells. Many of the spaces contained blood, all consistent with hemangioma.

involvement is more common than unilateral [1] and multiple digit involvement occurs in 50% of cases [3]. When more than one digit is involved, they are usually adjacent and the order of frequency in the hands is the index finger followed by middle finger and thumb; the ring and little fingers are seldom affected [1]. Order of frequency in the foot is second toe followed by third toe, first toe, then fourth and fifth toes, respectively.

Barsky [2] was also the first to note the almost invariable curvature of the involved digit toward the ulnar side, later explained by another study to be due to hypertrophy of the radial side of the digit causing the deviation toward the healthy ulnar side.

In macrodactyly there is soft tissue hypertrophy on palmar or plantar surfaces of affected digits causing the distal interphalangeal joints to be hyperextended, thus preventing flexion of the digit [5]. Increased size of the phalanges of involved digits is a primary feature of the anomaly with involvement of the metacarpals/metatarsals not always present [3].

Conclusion

Macrodactyly is not a familial disorder and is almost exclusively an isolated anomaly [3]. In the 167 cases reported in the literature, only one had known neurofibromatosis [3]. Another four cases were reported to have other associations: one had adrenal tumor and hemihypertrophy; one had epidermal nevus; one had multiple connective tissue nevi; and one had dysplasia epiphysealis hemimelica [3]. We believe our case is the first reported of macrodactyly involving both hands and one foot with associated cutaneous hemangiomata. With advancing age, the enlarged curved phalanges lead to osteophyte formation which causes early degenerative joint disease and pain.

Many theories have been presented describing this anomaly [1,3,5], and probably a combination of more than one defect plays a role in the pathology.

Treatment is usually unsatisfactory with soft tissue reduction with or without osteotomy being the main procedure [2-5] as was performed in our case.

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MITOCHONDRIAL DNA DELETION IN KEARNS-SAYRE SYNDROME: A REVIEW AND ILLUSTRATION OF CASES

Saeed Bohlega, FRCPC; M. Zuheir Al-Kawi, FAAN; Pamela Chavis, MD; Abdulrazzaq Haider, MD; Salah Omer, MRCP

Mitochondrial encephalomyopathies or mitochondrial cytopathies are a heterogeneous group of disorders that have widely variable clinical expression but share a common functional defect and morphologically similar mitochondria [1-4]. They are usually divided into three distinct clinical subgroups: (1) mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes (MELAS); (2) myoclonus epilepsy associated with ragged-red fibers (MERRF); and (3) chronic progressive external ophthalmoplegia (PEO) which includes Kearns-Sayre syndrome (KSS), a sporadically occurring multisystem disorder characterized clinically by chronic progressive external ophthalmoplegia, ptosis, pigmentary retinal degeneration, cerebellar dysfunction, and short stature [5-7]. Laboratory features of KSS include glucose intolerance, elevated cerebrospinal fluid protein, endocrine disorders, elevated levels of lactic acid in both serum and cerebrospinal fluid, and ragged-red fibers in muscle biopsies [8].

Large scale mitochondrial DNA (mtDNA) deletions have been described in a high proportion of patients who have a mitochondrial myopathy associated with PEO [9-13]. Such deletions now are considered the hallmark of KSS. Point mutation in the transfer RNA genes (leucine in MELAS [14-16] and lysine in MERRF [17]) have been recently identified which apparently interfere with mitochondrial translation. In this communication, we describe two patients with KSS in whom mitochondrial enzymes and mitochondrial deletion studies were performed.

Patient A

A 19-year-old Saudi male presented with progressive ptosis of five years' duration, proximal weakness and fatigability, nocturnal chest tightness and muscle cramps. Dysphagia was noted for two years. Intellectual deterioration forced him to stop attending school. He noted growth retardation and he was smaller than his younger brother. Family history was negative for muscle diseases.

Examination showed a slightly underweight male (weight 43 kg, height 155 cm). There were no skeletal abnormalities. Cognitive function was grossly normal. Visual acuity was 20/25 O.U. The optic discs were normal but pigmentary retinal changes were present (Figure 1). He had moderate

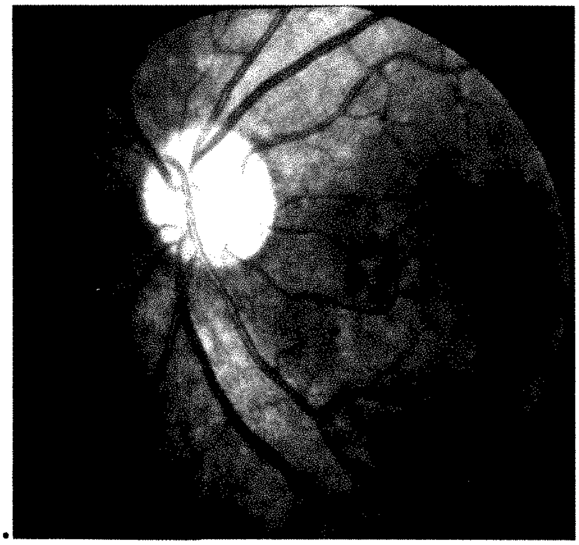

FIGURE 1. Atypical pigmentary change (patient A) "salt and pepper" retinopathy. Note fine sprinkling of retinal pigment which gives the fundus mottled hypopigmented and hyperpigmented appearance.

From the Departments of Medicine (Drs. Bohlega, Al-Kawi and Omer), Anatomic Pathology (Dr. Haider), King Faisal Specialist Hospital and Research Centre and Neuro-ophthalmology (Dr. Chavis) King Khaled Eye Specialist Hospital, Riyadh.

Address reprint requests and correspondence to Dr. Bohlega: Department of Medicine (MBC-46), Consultant Neurologist, King Faisal Specialist Hospital and Research Centre, P.O. Box 3354, Riyadh 11211, Saudi Arabia.

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bilateral ptosis with compensatory overactivity of frontalis muscles. External ophthalmoplegia was nearly complete and the pupillary response was normal. Orbicularis oculi, laryngeal, and neck flexor muscles were slightly weak. Hearing was intact. He had mild proximal limb muscle weakness. Cerebellar testing and tendon reflexes were normal. Mild respiratory muscle weakness was documented by pulmonary function tests.

Investigations: Blood count, urea, electrolytes and liver function were normal. Creatinine kinase was 135 IU (N: 25-195). Resting serum lactic acid was 2.7 mmol/L (0.5-2.0), serum pyruvate 90 units (30-80). Follicular stimulating hormone and luteinizing hormone were normal. He had decreased sperm count (19×10^6 sec/ml) with decreased motility and serum testosterone was decreased. Cerebrospinal fluid (CSF) protein was 550 mg/dl, with no oligoclonal bands on protein electrophoresis, IgG synthesis index was normal. Electrocardiogram (ECG) revealed first degree block and poor progression of the R wave in chest leads. MRI scan of the brain showed scattered bilateral white matter and basal ganglia lesions (Figure 2). Radiographs of the left hand revealed a bone age under 15 years.

Motor and sensory nerve conduction velocities and the response to repetitive nerve stimulation were normal. Motor unit potentials from biceps and deltoid muscles were short (20% decreased) and polyphasic (32% of all potentials). Left deltoid and left quadriceps muscle biopsies revealed some myopathic changes and scattered ragged-red fibers (Figure 3). Electron microscopy showed numerous abnormal mitochondria with bizarre pleomorphic shape, paracrystalline deposits, and osmiophilic inclusions.

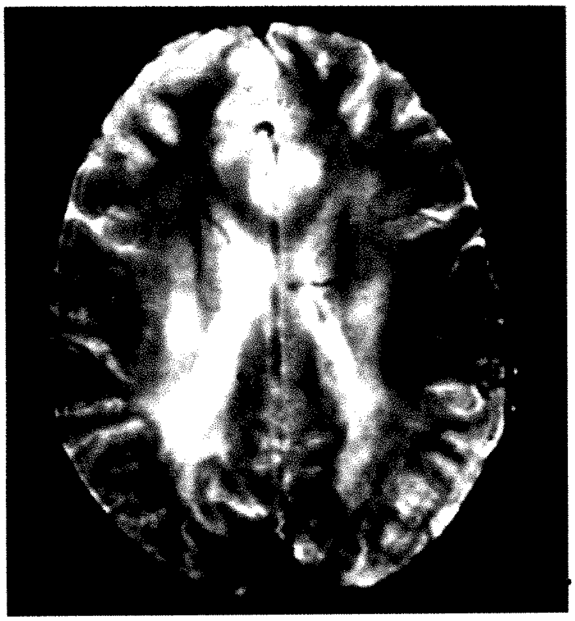

FIGURE 2. T2-weighted brain MRI showing deep white matter and basal ganglia lesions.

Patient B

A 25-year-old Saudi male presented with a 15 year history of progressive ptosis and restricted eye movements. At the time of admission, his major problem was fatigability and slow speech. Family history was negative for muscle disease. He was underweight (weight 46 kg, height 160 cm) and intellectually dull with a poor fund of knowledge. He had moderate retinal pigmentary changes without optic atrophy. There was moderate symmetrical ptosis with marked external ophthalmoplegia. Facial, neck flexor, and proximal limb muscles were mildly weak and the gag and cough reflexes were decreased. Tendon reflexes were hyperactive. Cerebellar testing and hearing were normal.

Investigations: Blood count, liver function tests, vitamin B_{12} level, serum folate, serum lipid profile, CK, thyroid function, acetylchloride receptor antibodies, serum pyruvate and serum ammonia were all normal. Serum lactic acid was 2.4 mmol/L(0.5-2.0). Pyruvate 83 mmol/L(30-80), aldolase 10.4 mmol/L(2-7). CSF protein was 1005 (N=150-450 mg/L). CSF lactic acid was 2.2 mmol/L(0.6-2.2). With exercise, he quickly became acidotic. Blood pH was 7.31 after peddling an exercise bike for three minutes. The ECG showed an interventicular

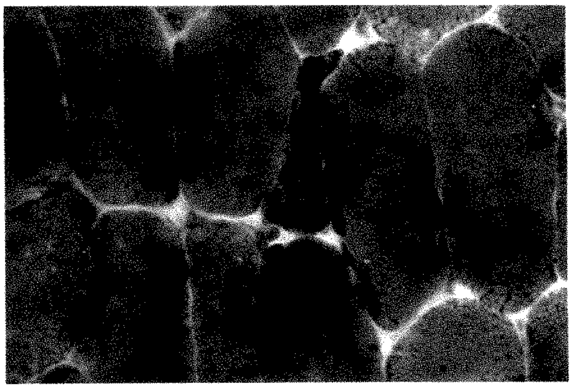

FIGURE 3. Modified Gomori trichrome stain shows ragged-red fiber.

conduction delay and poor R-wave progression on chest leads. The MRI showed moderate brain atrophy.

Motor unit potentials were myopathic. The response to repetitive nerve stimulation was normal. Deltoid muscle biopsy showed moderate myopathic changes with slight hypertrophy of Type II fibers. A few scattered ragged-red fibers were seen on modified Gomori trichrome stain. Electron microscopy showed abnormally large, bizarre, and pleomorphic mitochondria with paracrystalline deposits (Figures 4 and 5).

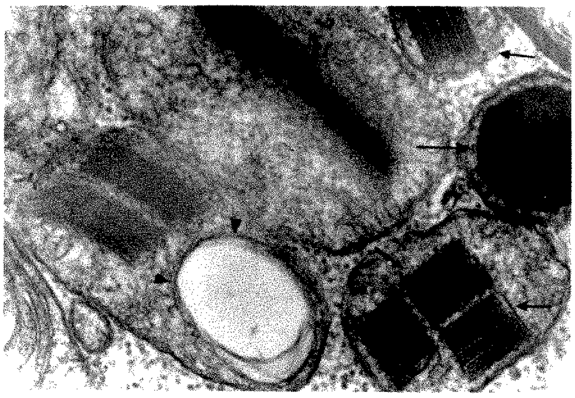

FIGURE 5. Abnormal collection of mitochondria showing paracrystalline inclusion (small arrow), osmiophilic inclusion (big arrow) and mitochondrial vacuoles (arrow heads) 50,000 x.

Determination of Mitochondrial Enzymes

Spectrophotometric assays as described by Di Mauro et al [18] were used to measure the enzyme activity of Cytochrome C Oxidase (COX), (Complex IV), Succinate Cytochrome C reductase (Complexes II and III), rotenone-sensitive NADH Cytochrome C reductase (Complexes I and III), NADH Dehydrogenase (Complex I), Succinate Dehydrogenase (SDH) (Complex II), and Citrate Synthase (a matrix enzyme) in crude muscle extract (Table I). The COX activity showed normal activity in both patients (see discussion) while the activity of other enzymes was generally high. DNA was obtrained from the whole muscle homogenate. The method described by Davis et al [19], was modified [10] to accommodate the small samples used. For Southern blot analysis, 5 mg of total DNA was digested with restriction enzymes (obtained from Boehringer Mannhein, New England Biolab Sigma and New England Nuclear) electrophoresed through a 0.8% agarose gel and transferred to nitrocellulose filters as described by Shanske et al [20]. The proportion of deleted mtDNA was estimated densitometrically as outlined by Zeviani et al [21], (Figure 6).

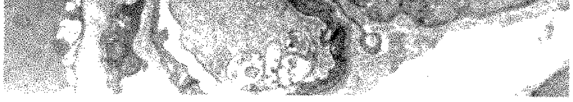

FIGURE 4. Electromicrograph showing an increased number of mitochondria in the subsacrolemmal region of one muscle fiber, up and right, compared with relatively normal looking muscle fiber in the left part of the figure. Note (1) abnormal proliferation of the mitochondrial cristae (arrow heads), (b) abnormal mitochondria with "paracrystalline" inclusions (small arrow) 25000 x.

To identify the site of the deletion, DNA was digested with a battery of restriction enzymes Echo RI, Hind III, PstI, and XbaI. The patterns obtained after Southern blot hybridization were analyzed based on the published human mtDNA sequence [22], (Figure 7).

TABLE I. *Mitochondrial enzyme activities in isolated muscle mitochondria.**

	Patient A	Patient B	Control (Mean ± SD)*
1. Cytochrome C oxidase (Complex IV)	2.770	4.063	2.80 ± 0.52 (71)
2. Succinate-cyt C reductase (Complexes II + III)	1.048	1.372	0.701 ± 0.228 (69)
3. NADH-cyt C reductase (Complexes I + III)	0.800	1.069	1.02 ± 0.377 (78)
4. NADH-cyt dehydrogenase (Complex I)	29.79	21.29	35.48 ± 7.07 (76)
5. Succinate dehydrogenase (SDH) (Complex II)	2.709	2.626	1.00 ± 0.526 (78)
6. Citrate synthase (umoles/min/gm)	12.90	17.80	9.88 ± 2.55 (73)

Enzyme activities are expressed as μmol/min/mg fresh tissue. Control values are mean ± SD, number of control in parenthesis.

Discussion

Drachman coined the term "ophthalmoplegia plus" [6] to describe a group of patients with PEO, limb weakness and various other features reflecting disturbed function of brain, peripheral nerve, eye, heart, or endocrine system. KSS represents a subgroup of ophthalmoplegia plus and is defined clinically by the invariable triad: (1) onset before the age of 20; (2) progressive external ophthalmoplegia; and (3) pigmentary retinopathy plus at least one of the secondary triad: (1) cardiac conduction defects; (2) CSF protein of 100 mg/dl or more; and (3) a cerebellar syndrome. Other abnormalities have been found in patients with KSS, including mental retardation, Babinski sign, limb weakness, hearing loss, seizures, short stature, delayed puberty and various endocrine abnormalities [2,8,23]. Ptosis is usually the presenting symptom and starts as early as age two. Ophthalmoplegia affects all muscles equally and never involves the pupils.

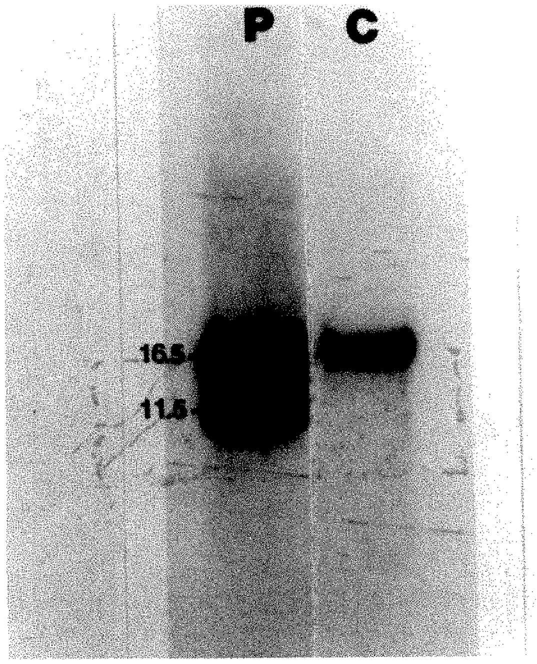

FIGURE 6. Southern blot (patient B) P, and control C. DNA was digested with Pvu II, electrophoresed through a 0.8% agarose gel, transferred to nitrocellulose and probed with labeled mtDNA. These are two hybridizing bands - a normal size mtDNA of 16.5 kb and a more rapidly migrating band (11.5kb) due to a deletion of approximately 5 kb.

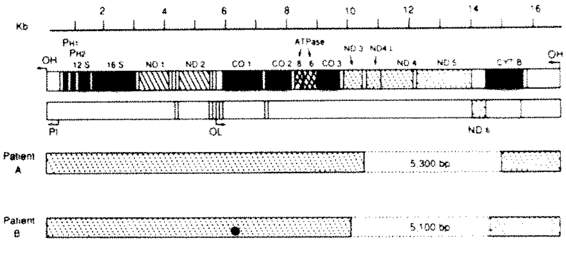

FIGURE 7. Localization of mitochondrial DNA deletions. The linearized map represents the heavy (upper) and light (lower) strands of mtDNA [21] showing the genes for the subunits of NADH-coenzyme Q reductase (ND), cytochrome c oxicase (CO), cytochrome b (CYTB), ATP synthase (ATPase), and for the 12S and 16S ribosomal RNAs. The transfer RNAs are denoted by small open boxes. The origins of heavy-(OH) and light strand (OL) and the promoters for initiation of heavy (P_{H1} and P_{H2}) and light strand (P_{l}) transcription are indicated by the arrows. Muscle mitochondrial DNA from patients A and B are represented by the bars. Intact regions are shown as solid areas. Deleted fragments are shown as open (dotted) areas. The numbers within these areas indicate the size of the deletion. Scale on top in kilobase (kb).

The retinopathy usually affects the posterior fundus and has a salt-and-pepper appearance with diffuse depigmentation of the retinal epithelium. It is called atypical to distinguish it from the typical perivenous, bone spicule appearance of retinitis pigmentosa [24]. The clinical course is usually benign with night blindness or diminished visual acuity occurring in less than half of the patients [8,24].

The onset of heart block occurs months or years after established ophthalmoplegia. The conduction disturbances worsen sequentially from interventricular conduction defects to bundle branch block, trifascicular disease and finally complete heart block which may cause sudden death.

Cerebellar dysfunction and mental retardation vary from mild to severe. Histopathology of the brain in KSS shows spongy degeneration of white and gray matter, affecting cerebellum and brainstem, including the oculomotor nuclei [7]. On MRI these changes appear as hypodense lesions in the cerebral white matter [25]. However, information is limited because many patients have a pacemaker which precludes MRI examination. The diffuse white matter disease seen in our patient (Figure 2) is presumably related to the spongy degeneration noted histopathologically [25].

The morphologic hallmark of mitochondrial myopathy is the presence of ragged-red fibers in muscle biopsies stained with the modified Gomori trichrome stain (Figure 3). The blotches of stain giving the "ragged-red" appearance are due to an abnormal proliferation of mitochondria. Electron microscopy demonstrates clusters of abnormally enlarged and elongated mitochondria containing increased irregularly oriented or whorled crystals.

These are usually more abundant under the sarcolemma (Figure 4). Some mitochondria contain characteristic "paracrystalline" or dense osmiophilic inclusions, the former appearing square or rectangular in shape with geometric lattice appearance (Figure 5). These appear to be composed of abnormal proteins [1,3].

Biochemical studies of the mitochondrial metabolism in some affected individuals have revealed normal respiratory chain function [9,26] while others show a heterogenous defect of either Complex I [4], II [27], IV [28,29], V [4], or multiple defects [10,12].

Mitochondria are unique among cellular organelles in that they contain their own DNS (mtDNA) which can be transcribed and translated to form proteins. Human mtDNA is small (16.5 kilobase), circular, double-stranded (heavy and light strands) and has been fully sequenced [22]; mtDNA codes for the components of the mitochondrial respiratory chain, the oxidative phosphorylation systems, 2 ribosomal RNAs and 22 transfer RNAs [30]. Most other mitochondrial proteins are encoded by nuclear DNA, synthesized in the cytoplasm and then directed to the appropriate mitochondrial compartments [18]. A mitochondria contains 2-10 copies of the mtDNA genome. An individual would inherit mitochondria from the mother via the ovum cytoplasm (maternal inheritance). During mitosis the mitochondria segregate randomly into each daughter cell (mitotic segregation). Unlike nuclear DNA, there is a high frequency of mutation and no repair in mtDNA [31].

Several recent investigations of mtDNA structure in progressive ophthalmoplegia and KSS have revealed large deletions of mtDNA in a subset of patients [9,13]. Deletions are found in 80% to 90% of patients with KSS and 40% of patients with ocular myopathy [9,10]. The inability to detect a mitochondrial deletion does not exclude the possibility of a mitochondrial genomic abnormality because of the inherent limitation of restriction analysis [35]. Endonuclease analysis could miss a deletion of less than approximately 100 base pairs or a point mutation [9].

Deletions range from 1.3 to 7.6 Kb constituting 8% to 55% of the length of intact mtDNA. Many map to an identical region of mtDNA, suggesting that there are "hot spots" in the mitochondrial genome [9,10] that are especially prone to deletion. The deletions are thought to arise by spontaneous mutation of mtDNA in the oocyte or zygote rather than pre-existing in the mother. Mothers of patients with KSS do not have detectable mtDNA deletion in their muscle biopsy specimens [9,12,13].

The number of affected mitochondrial genome in patients with PEO varies from 27% to 85%. The percentage of affected mitochondrial genome differ in different tissues from the same patients as well [20]. This suggests that expression of a mitochondrial disease may require a threshold number of mutated mtDNA [10,32]. It is not known why ophthalmoplegia is the invariable manifestation of mtDNA deletions. It is theorized that since the external ocular muscles are derived from only a few embryonic cells, they will have a large number of mutated mtDNA. The mitochondrial volume fraction in eye muscles is three to four times that of limb muscles [9]. On the other hand, the functional effects of deleted mtDNA in eye muscles will be substantially greater as the metabolic demands of these muscles are high [12]. The findings that identical deletion can be associated with both KSS and pure ocular myopathy led Moraes et al [10] to suggest that KSS is the full expression of a pleiotropic disorder. The different clinical phenotypes are presumably related to the phenomenon of "mitotic segregation" [31] in which there is random partitioning of mitochondria into daughter cells during early cell division causing some cells to retain a mixture of wild and mutant DNA (heteroplasia). Thus, the percentage of affected mitochondrial genome differs in various tissues from the same patients [20,33,34]. In pure ocular myopathy, mtDNA deletion has been found in amounts much smaller than in KSS; detectable only by polymerase chain reaction amplification [33]. Therefore, the difference in clinical severity and organ involvement between KSS and ocular myopathy seems related to the number of deleted mtDNA in various tissues. Involvement of an organ or structure occurs when a "threshold" number of abnormal mtDNA are present.

The activity of four of the six mitochondrial enzymes (Numbers 1 to 4, Table 1), was significantly lower in KSS patients with deletion than in patients with PEO and no deletion [10]. These four enzymes are part of the respiratory chain complexes and are contained in one or more subunits encoded by mtDNA. This indicates that the entire mitochondrial genome function as a single genetic unit rather than a series of genes encoding individual enzymes.

However, Holt et al [9] and others [9,11,26,34] noted some patients, like ours, with mtDNA deletion and normal mitochondrial-enzyme activities. This apparent inconsistency between the biochemical defects and the molecular lesion may be due to the focal nature of the disease [26], or segregation of affected and normal mtDNA among mitochondria [16].

Therefore, the exact relationship between mtDNA deletion and the clinical or biochemical phenotype remains to be clarified.

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Letters to the Editor

The *Annals of Saudi Medicine* welcomes letters to the Editor from its readers. They may be on any topic, though the Editor especially encourages discussion of papers published in the *Annals*. Letters should be no more than 100 typewritten lines in length, typed double-spaced, and submitted in triplicate. Letters may include one figure or brief table and up to five references. Submission of a letter constitutes permission for the *Annals* to use it for publication. Letters should not duplicate similar material being submitted or published elsewhere and the *Annals* reserves the right to edit letters submitted. Letters referring to a recent *Annals* article should be received within six weeks of the article's publication.

HCV In Hemodialysis Patients In Benghazi, Libya

To the Editor: The prevalence of hepatitis C virus (HCV) infection in hemodialysis patients in Benghazi, Libya was assessed in sera from 47 patients who were attending the dialysis unit in the 7th April Hospital, Benghazi, Libya with an enzyme immunoassay (Abbott Diagnostic System).

Anti-HCV was found in 20 (42.5%) patients. The seropositive anti-HCV was confirmed by polymerase chain reaction (PCR) in 17 (36.1%) patients. The prevalence of HCV markers are further studied with relation to age of the patients. Only one patient (2%) had an increased serum bilirubin at the same time; this patient's serum was negative for HBsAg (ELISA, Sorin Biomedica), suggesting that this abnormality was most likely due to HCV infection. Only 4 (8%) patients had an increased alanine aminotransferase (ALT) and were thought likely to have been exposed to non-A, non-B hepatitis (NANBH). This indicates that using ALT as a surrogate marker for NANBH is inappropriate. The prevalence of anti-HCV found in Libyan hemodialysis patients is 40 times higher than that found in other blood donors [1].

There was a correlation between anti-HCV positivity and the use of blood transfusions or blood products in all positive patients. On the other hand, several seronegative patients had previously received between eight and 20 separate transfusions. Our anti-HCV prevalence of 42.5% is higher than the prevalence found in patients in Saudi Arabia [2] and Germany [3]. The reason for this difference is as yet unknown. It is possible that this may be due to the higher sensitivity of our method of detection of anti-HCV (Abbott ELISA, second generation) compared to theirs (Ortho ELIAS, first generation), which has been known to give false results in some circumstances such as stored sera, rheumatoid factor positive and in certain lipoproteins [1]. Eight (40%) of the 20 seropositive anti-HCV patients were also carriers of HBsAg. However, evidence of previous hepatitis B exposure was present in 18 (90%) of the 20 anti-HCV positive patients and in 17 (62.9%) of the 27 anti-HCV negative patients (x^2=4.41 P 0.05).

In conclusion, our findings suggest that control of HCV infection in the hemodialysis unit of Benghazi, Libya is imperative.

Abdul-Naser Y. El-Zouki, MBBS
Al-Arab Medical University
Benghazi, Libya
Awad B. Bendard, MD
Mohamed S. Sharif, MBBS
7th April Hospital
P.O. Box 7224
Alberka Post Office
Benghazi, Libya

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General Anesthesia for Cataract Surgery: Experience at King Fahd Hospital of the University

To the Editor: Umeh and Tamimi [1] have presented a thorough review of 92 patients having cataract surgery under general anesthesia, emphasizing that despite the significant pre-existing medical ailments of many of these patients, none experienced mortality or significant morbidity from general anesthesia. These results are reassuring to those of us who are, at times, hesitant to utilize general anesthesia for such patients, but feel compelled to do so because of the patient's inability to lie flat or because of a communication barrier between the patient and anesthesiologist. However, I point out another conclusion that can be drawn from the authors' data. It is easy to overlook the fact that an estimate of the true incidence of a serious complication in an entire population can be estimated from a small series, even when the numerator is zero (i.e., the complication did not occur in the series) [2]. This is given by the formula $R=1-P$ divided by n where R=the complication rate, P = P value and n = number of patients [3]. In this case, involving 92 patients and a zero incidence of mortality or serious morbidity, the true population rate of complications, with 95% confidence (or a P value of 0.05), can be estimated at no more than 1 in 30.67 or 3.26%. In a high risk population such as the authors', this probably compares favorably with the risks of local anesthesia and sedation noted in other series [4].

The opinions and views expressed here do not necessarily represent those of the Department of Defense, the Department of the Air Force, or any other agency of the government of the United States of America.

Major Karl A. Poterack, MD, USAF
Chief, Neuroanesthesia Service
Wilford Hall USAF Medical Center
Lackland AFB, TX, USA, 78236

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Reply

To the Editor: We appreciate Dr. Poterack's comments and welcome the opportunity to respond to them.

We did not use the formula mentioned by Dr. Poterack in his statistical analysis of our data; but the low risk value of 1-30.07 or 3.26% obtained from his calculation confirms our finding that a properly conducted general anesthesia in patients in optimal physical health for cataract surgery probably carries no more risk than local anesthesia with sedation.

Beatrice Umeh, FFARCS
Elham Tamimi, FKFU
Department of Anesthesiology
King Faisal University Dammam
King Fahd Hospital of the University
P.O. Box 40037
Al-Khobar 31952, Saudi Arabia

Brucellosis in Pediatric Patients: A Review of 114 Cases from Asir Region

To the Editor: I read with interest the report on brucellosis in children by Nabi and Mir [1]. The objective of the study was to highlight brucellosis as a major cause of morbidity in the pediatric population of the Asir region. The authors mentioned paucity of data on its clinical pattern in Saudi children. This is true; however, they could have quoted two additional reports published from Saudi Arabia [2,3].

In our study of brucellosis in children in Gurayat, a small peripheral town in the northwestern region of Saudi Arabia, a total of 55 children were diagnosed over a period of one year from March 1988 to February 1989. A total of 23 cases were admitted to Gurayat General Hospital and comprised 1.4% of a total of 1672 pediatric admissions. An additional 32 children were diagnosed and treated in the outpatient clinic of the hospital during the same period. Thirty-one (56%) patients were male, all were Saudi nationals, mean age was 5.94 years (range 5 months to 12 years, median 6 years), and 26 (47%) were younger than five years of age (Table 1).

Brucellosis prevailed throughout the year, with 41 (75%) cases diagnosed during the summer months from March to August. All but one patient presented with unexplained fever for more than one week, 18 (32%) had arthralgia or arthritis. All the patients had a history of raw milk ingestion or close contact with sheep, goats, camels, or contact with infected family members. As in the previous studies, B. melitensis was the major pathogen on serological examination [1-3]. All the patients were treated with a combination of Septrin (trimethoprim) 7-10 mg/kg/day, sulfamethoxazole 30-50 mg/kg/day, and rifampicin 20 mg/kg/day. Duration of treatment was 4-6 weeks, with a longer duration being given to children with severe disease with or without arthritis. One child was given added injections of streptomycin for an initial period of two weeks. No

TABLE 1. *Age distribution.*

	Age in months				
	5 - 11	12 - 35	36 - 59	60 - 144	Total
No	8	8	10	29	55
%	14.5	14.5	18	53	100

child had any neurological or cardiac complications or death. One child required repeat admission because of relapse. Frequently, more than one family member was affected. In one family, six children were affected. One child presented four months following diagnosis in the other five siblings. I concur with the authors that rifampicin and trimethoprim are an encouraging combination therapy. In Gurayat there are 20,000 children, 40% of a total population of 50,000. This gives an annual incidence of 2.75/1000 children. Up to 20 or more cases may occur for each reported case [4], making the actual prevalence higher in this region.

Brucellosis is a preventable disease and in view of the magnitude of the problem in children, there is an urgent need for an effective control program. There is agreement that control of human brucellosis is through the control of it in animals. It has been found that widespread vaccination of sheep and goats has proven to be very effective in reducing human brucellosis. It is the veterinarian's responsibility to accept the challenge to control animal brucellosis, which in turn will control the disease in humans [5].

AKM Harunur Rashid, MRCP(UK), DCH
Consultant Pediatrician
Suleimania Children's Hospital
P.O. Box 59046
Riyadh 11525, Saudi Arabia

References

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Scorpion Envenomation in the Children of Northwestern Saudi Arabia

To the Editor: We read with interest the report of Izuora et al regarding their experiences involving scorpion stings in children located in Marjadah, Saudi Arabia [1]. As a comparison, we present our experiences in a retrospective review of scorpion envenomation in children admitted over a two year period from January 1988 to December 1989 at Gurayat General Hospital located in the Northwestern region of Saudi Arabia.

During this period, a total of 3305 children were admitted to the pediatric ward. Of these, 51 (1.5%) children were admitted due to scorpion sting. There were 24 boys as compared to 27 girls. Age ranged from 8 months to 13 years. A total of 22 (43%) children were younger than five years of age. In the previous studies conducted in Baha [2] and Eastern Riyadh [3], seasonal variations were observed. There were only 5 (10%) admissions during the winter period from October to March compared with 35 (69%) admissions during the extremely hot period from June to August. Common clinical signs and symptoms were mild to intense pain, erythema, swelling, tingling, tachycardia; moderately toxic children presented with restlessness, abdominal distention, frothing salivation, and vomiting, in addition to local findings at the puncture site. The majority of children presented within six h of the sting. A total of seven (14%) children stayed ≤ 24 h, 28 (55%) stayed from 25-48 h, 13 (25%) stayed 49-72 h, and only 3 (6%) stayed more than 72 h in the hospital. Four children were admitted directly to the intensive care unit (ICU) with severe restlessness, hypersalivation and convulsions. Two of these chidren were male, one age four years and two months; the other was six years of age; both had convulsions, became comatose, and died within 24 h of admission. The six-year-old child became hyperpyrexic, developed disseminated intravascular coagulopathy (DIC), shock, and ventricular fibrillation. This gives a mortality rate of 4% compared to 2.3% in adult patients in Baha [2] and 25-50% in children elsewhere throughout the Middle East [4]. From the list of scorpions found in Saudi Arabia [5], it is evident that toxic varieties are present in the Al-Gurayat area. We did not make a systematic attempt at identification of the various scorpions in this retrospective study. However, the description by the parents and a few specimens brought in by them fit either the Apistobuthus pterygocercus or leiurus
quinquestriatus.

All the patients in our series routinely received scorpion antivenin. Other supportive measures included an antihistamine and topical 2% xylocaine injection. Intravenous diazepam 0.3 mgm/kg was occasionally used to treat children with severe irritability or convulsion. The two children who died in the intensive care unit received diazepam, dopamine, and other life support including ventilation, in addition to scorpion antivenin. Although the effectiveness of the scorpion antivenin has been in doubt [2,6], this was routinely administered to all our patients. In view of the rural location of our hospital and the insufficient facilities for observation in the Emergency Room, we choose to be cautious and liberal with our admission policy as noted by Izuora et al, even though some of our patients did not require hospitalization [1]. Miller reported that deaths from scorpion stings occur, particularly in children younger than four years of age[7] but demonstrates that a fatality can occur at any age. During hospitalization, none of our children deteriorated after looking stable at presentation. Brennan et al were unable to document any bleeding in any of the 86 adult patients in their care, although seven patients had slightly abnormal coagulation tests [2]. However, one of our patients developed gross hematemesis and melena due to DIC and died. It appears that although there have been no mortality reports from Marjadah [1] or Eastern Riyadh, scorpion sting envenomation can be fatal. Therefore, precautionary measures may help to avoid the rather high mortality rate reported in children in the Middle East [4].

AKM Harunur Rashid, MRCP(UK), DCH
Mohamed Ishtiaque Hossain, MBBS
Suleimania Children's Hospital,
P.O. Box 59046
Riyadh 11525, Saudi Arabia

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Reply

To the Editor: We wish to thank Rashid and Hossain for their interest in our paper on scorpion envenomation in Marjadah children, Asir Region [1]. Their experience on the same topic in children in the Northwestern region of Saudi Arabia [2] conforms, essentially, with the pattern found in other parts of the Kingdom [1,3,4], as far as general clinical manifestation and complications are concerned.

The statement in our paper that children below the age of four years are more susceptible to the effect of scorpion sting [5] does not necessarily exclude the possibility of severe complications and death beyond this age as shown in their study [2]. In our review [1], although mortality was nil, eight out of 19 children who presented with severe symptoms were in the age group 4-12 years. What perhaps is more significant is that the duration of symptoms is inversely related to the patient's age [6]. Furthermore, it appears likely that the effect of the same quantity of toxin introduced by a sting will be more lethal in an infant or toddler than an older child or adult.

The issue of consumption coagulopathy complicating scorpion sting in one of their patients who died is quite intriguing. The study by Brennan et al on adults who were stung by scorpions revealed only mild abnormalities in the coagulative functions of the blood[4], whereas El-Amin and Ul-Din-Khan did not encounter any hematological problems in a prospective study on children [7]. Without outright dismissal of the possibility of severe hematological dysfunction in scorpion envenomation, it must be borne in mind that several other clinical conditions including shock, acidosis, and hypoxia may also induce disseminated intravascular coagulopathy (DIC).

In conclusion, it cannot be overemphasized that careful monitoring of affected children is very vital and that overtreatment can be counterproductive. According to Neale [3], "conservative symptomatic management is the most desirable" and Rimsza et al [6] warn against the "temptation to totally control the restlessness" of a child with scorpion envenomation.

G. Ike Izuora, MD, DTM&H, FA
Department of Pediatrics,
Northern Area Armed Forces Hospital,
Hafar Al Batin, Saudi Arabia
Anis Ali Syed, MBBS (Pb), MCPS (Pak)
Al Hindi Almahdi, MBBCH
General Hospital Marjadah,
Asir Region, Saudi Arabia

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Urological Cancers in Asir Region

To the Editor: Due to the lack of a national cancer registry in Saudi Arabia, information on the incidence and prevalence of various cancers is, at present, unavailable [1]. However, reports from various hospital-based studies [2] such as ARAMCO, Al-Baha, and Asir [3] shed some light on the magnitude of the problem. We have retained an oncology registry in which all urinary neoplasms have been entered in the Department of Urology in Asir Central Hospital, Abha, during the past five years. We have analyzed the first 100 patients in an attempt to study the crude relative frequency and rank order. The registry represents the majority of patients with urological cancers in this region, although several patients were referred to other referral centers. Since all referring urologists are aware of the registry, most patients they see are referred to this hospital for cancer care with the size representative of the cancer pattern. All bladder, prostate, and renal cancers have been histologically confirmed and staged according to TNM classification. Bladder cancers were divided into bilharzial and non-bilharzial according to the presence of histological stigmata of bilharzial pathology. Prostate specimens were obtained by either transurethral resection or perineal/transrectal needle biopsies. The mean age and tumor stage at presentation were compared in the commonly seen urological malignancies.

TABLE 1. *Rank order and relative frequency of various urological cancers .*

Rank order	Type of Cancer	No.	%
1	Bladder	50	50%
2	Prostate	20	20%
3	Kidney	16	16%
	a) Renal cell carinoma	11 (69%)	
	b) Pelvicalyceal	3 (19%)	
	c) Nephroblastoma	2 (14%)	
4	Testis	7	7%
5	Ureter	3	3%
6	Peno-pubic	3	3%
7	Adrenal	1	1%
Total		100	100%

Common urological malignancies seen in order of frequency were bladder 50%, prostate 10%, renal 16%, and testicular 7%. Of all renal malignancies, renal cell carcinoma was the most common (69%) seen. Extensive scarring resulting from major genital skin degloving at circumcision i.e., "Tihama Circumcision" was the cause behind the occurrence of three penopubic squamous cell carcinomas. This is similar to Marjolin's ulcer which begins in the scar tissue following the ritual circumcision practiced in the lowlands of the Asir region called Tihama. The classical penile cancer seen elsewhere was not seen in this series.

The mean ages for bladder, prostate, and kidney cancers were 65.5, 72.2, and 56.6 years, respectively. For bilharzial bladder cancers in males, mean age (50 ± 7.59 years) was significantly lower than that of non-bilharzial bladder cancer (62.36 ± 14.3 years) , (P <0.05) and that for testicular cancer was 28 years. However, a 70-year-old patient with non-Hodgkin lymphoma of the testis was encountered. Male to female ratio for bladder and renal cancers were 5:1 and 1:1, respectively.

As far as histological pattern of neoplasm, 74% of bladder cancer was transitional cell carcinoma (TCC) despite the region being endemic for bilharziasis, 22% squamous cell carcinoma (SCC), and 4% adenocarcinoma (ADC). Only 10 (20%) were bilharzial bladder cancers out of which eight (80%) were SCCs and 2 (20%) ADCs, but none were TCC. All of the prostatic cancers were ADC. Out of 16 renal cancers, 11 (69%) were renal cell carcinomas, three (19%) were TCCs of the renal pelvis, and two (12%) were nephroblastomas, which is comparable to figures from other areas in Saudi Arabia. Out of seven testicular tumors, only three (43%) were seminomas. The only adrenal tumor was a pheochromocytoma. All penopubic cancers were SCCs.

Among 20 prostatic cancers, 19 were found in Saudis and ranked as the tenth main cancer in this region.

There was a general trend for late presentation of neoplasms at different sites. Advanced disease was seen in 80%, 85%, 57%, and 71% of bladder, prostate, kidney, and testis, respectively, which compares with the findings of Hanash et al [4].

Among several reports regarding cancer in Saudi Arabia [2], only a few dealt with cases originating in a single region such as Al-Baha, ARAMCO, and Asir [3]. Larger series from the main referral centers in Riyadh do not reflect the true frequency of various cancers at the regional levels [2,5,6]. Taylor reported on 264 cancer patients seen over a ten year period from ARAMCO and 5.6% were urological, four of whom were vesical. A similar review of 11,204 cases from King Faisal Specialist Hospital and Research Centre (KFSH&RC), in Riyadh [6] reported that 6% of all cancers were urological. However, the frequency was different i.e., bladder cancer 41%, kidney 28%, prostate 18%, and testis 13%, which is comparable to our findings. In the Asir region, 7% of all cancers seen in Saudi citizens were urological [2].

We wish to draw attention to the fact that bladder cancer is the most common urological cancer in the Asir region. In spite of being an endemic bilharzial zone, most of these cancers were non-bilharzial cancers. The majority of patients with bladder, prostate, renal, and testicular cancers present at an advanced stage and hence, the available treatment options are few. Public health education may lead to early disease detection and better treatment management. The need for a well documented regional cancer registry cannot be overemphasized.

Sugandh D. Shetty, MS, FRCSE, FRCS
Ahmed I.A. Ibrahim, FRCSE
Department of Surgery
Division of Urology
King Saud University - Abha Branch
College of Medicine
Krishna P. Patil, MCh, FRCSE
Nagalingam Anandan, FRCSE
Suhayl Al-Kotob, Fachartz
Shafique R. Memon, MBBS
Asir Central Hospital
Abha, Saudi Arabia

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Paraganglioma of the Spermatic Cord

To the Editor: Pheochromocytoma is a rare endocrine tumor arising in the sympatho-adrenal system from chromaffin cells which occur in close association with celiac, mesenteric, renal, adrenal, hypogastric, testicular, and paravertebral sympathetic plexuses [1]. It typically secretes epinephrine, norepinephrine, or both. The incidence is about 1.35/100,000 of the general population [2] and occurs in less than 1% of all hypertensive patients. In most large series reported, the incidence of malignancy is 10-15%. Ninety percent of pheochromocytomas arise in the adrenal medulla and the remaining 10% are extra-adrenal pheochromocytomas (paragangliomas) [2], where malignancy is quite frequent. Less than 2% of paragangliomas occur in the neck, thorax, and posterior wall of the atria. Children have a higher incidence of extra-adrenal tumors which are frequently multiple and bilateral, and can occur anywhere from the base of the skull to the gonads [2]. The most common locations are the renal hilum, peri-aortic region, and the organ of Zuckerkandl [2]. Only one case of paraganglioma of the spermatic cord has thus far been reported in the English literature [3]. The present case is the second, as far as can be determined.

A 37-year-old married Pakistani driver and father of three children presented with a nine-month history of a right scrotal swelling. The swelling became painful and increased in size during the seven month period prior to admission. There was no history of trauma, fever, weight loss, or loss of appetite. There were no respiratory or urinary tract symptoms.

On examination, the patient looked healthy, was neither anemic nor jaundiced. His pulse rate was 74 beats/min and blood pressure 120/80 mm/Hg. Abdominal examination revealed no abnormalities. The only abnormal finding was a firm, lobulated, oval, non-tender, non-reducible mass measuring 10 cm x 4 cm in the right spermatic cord, contiguous with the testis and epididymis. The right spermatic cord was thickened. Testicular sensation was intact and the scrotal skin was freely mobile over the mass. It did not transilluminate. The contents of the left scrotal sac were normal. There was no inguinal lymphadenopathy. Rectal examination revealed no abnormality.

Complete blood count, random blood sugar, urea, electrolytes, liver function tests, and erythrocyte sedimentation rate were all normal. Chest x-ray, electrocardiogram, and urinalysis were also normal. Urine culture yielded no growth. Tuberculin test was, however, strongly positive.

A provisional diagnosis of tuberculous epididymo-orchitis was made. A biopsy of the mass revealed polyhedral cells with eosinophilic granular cytoplasm. The cells were arranged in an alveolar septate pattern with highly vascular stroma (Figure 1), suggesting a diagnosis of paraganglioma.

Abdominal and hepatic ultrasonography, computed tomographic (CT) scan of chest, abdomen, and pelvis, as well as intravenous urogram (IVU) and 24-h urinary vanillylmandelic acid (VMA) were normal.

Right epididymo-orchiectomy was performed. Histopathology of the resected tumor was similar to that of the biopsy specimen. Electron microscopy showed few small, round, dense granules in the cytoplasm.

Immunohistochemical test using the peroxidase-antiperoxidase technique revealed the presence of neuron specific enolase (the neuroendocrine cell marker) in the cytoplasm of the tumor cells. This further supports the diagnosis of paraganglioma.

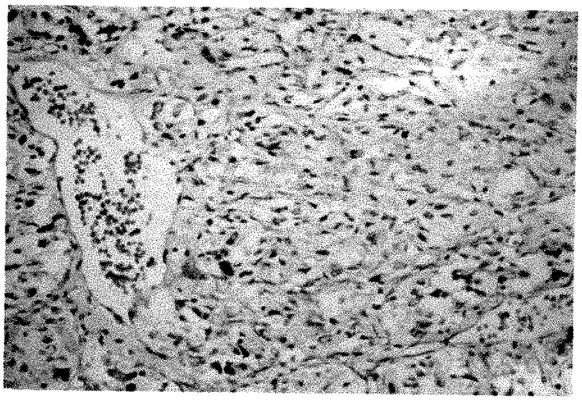

FIGURE 1. Photomicrograph showing a representative area from the paraganglioma, magnification 100 x.

Postoperative VMA assay at six month interval was negative.

Discussion

Paragangliomas are not common. When they occur in unusual sites, they may be overlooked, especially in the absence of the usual biochemical markers.

Similarly, tumors of the spermatic cord are not common. Most of these are easily recognized lipomas. However, 20% are malignant and most are sarcomas, carcinoma being very rare [5].

A paraganglioma of the spermatic cord is, therefore, a rarity that merits reporting in order to stimulate clinical awareness of its occurrence. Because of the tendency of recurrence *and* the greater propensity of paragangliomas for malignancy, careful total epididymo-orchiectomy is the treatment of choice. A six-month follow-up to monitor recurrence is essential.

In conclusion, a case of paraganglioma of the spermatic cord is presented. Although this would appear to be only the second such case to be recorded, nonetheless, spermatic cord paraganglioma should be carefully thought about.

Thirty-six months following excision, urinary VMA showed no evidence of recurrence. Life-long follow-up with annual urinary catecholamine evaluation is considered to be mandatory [4].

Acknowledgment

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Faisal Mashat,* FRCS(I), FRCS (Ed), FICS
Abdulrahman Meccawi, FRCS(Ed)
Department of Surgery
Shivraj Garg, FRCS(Glas), FICS
Edward Christian, FRCPath (Eng)
Departments of Surgery and Pathology
King Abdul Aziz University Hospital
P. O. Box 6615,
Jeddah 21452, Saudi Arabia

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Change of Address

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Announcements

The *Annals of Saudi Medicine* is pleased to publish announcements of educational opportunities of interest to its readers. For adequate publication layout time for publicity, notices of postgraduate schedules, courses, meetings, and lectures must be received at least **six months prior** to the date of occurrence. Please send relevant information to Mary Anne De Santis, Senior Editor, *Annals of Saudi Medicine*, Publications Office (MBC-36), Academic Affairs and Postgraduate Education, King Faisal Specialist Hospital and Research Centre, P.O. Box 3354, Riyadh 11211, Saudi Arabia. Tel.:464-7272 extensions 1815/1816; Fax:(01)442-7237.

King Faisal Specialist Hospital and Research Centre Postgraduate Training Programs

King Faisal Specialist Hospital and Research Centre is pleased to invite applications for the following full-time postgraduate training programs:

1. Arab Board residency training in the specialties of internal medicine, obstetrics/gynecology, pediatrics, and surgery.

2. Five-year pathology residency training program affiliated with King Saud University, the Royal College of Pathologists of Australasia and the Royal College of Pathologists of Great Britain.

3. Fellowships are offered in the following areas: Cardiovascular Diseases; cardiology, pediatric cardiology, thoracic and cardiovascular surgery. Oncology; hematology, medical oncology, and pediatric hematology-oncology. Medicine; endocrinology, gastroenterology, infectious diseases, nephrology, pulmonology, critical care, and rheumatology. Pediatrics; allergy and clinical immunology, neonatal/perinatal medicine, gastroenterology and hepatology, infectious diseases, nephrology, neurology, genetics, metabolic diseases, and endocrinology.

For further information, contact: Director, Academic Affairs and Postgraduate Education (MBC-36), King Faisal Specialist Hospital and Research Centre, P.O. Box 3354, Riyadh 11211, Saudi Arabia; Tel.:(01)442-7214, or Fax:(01)442-7237.

King Faisal Hospital and Research Centre Academic Calendar for 1413H/1993G

King Faisal Specialist Hospital and Research Centre has scheduled the remaining Academic Calendar for 1413H/1993G:

USMLE (Step 2)	7-8 Shawwal 1413 (30-31 March 1993)
USMLE (Step 1)	18-19 Dhu Al-Hijjah 1413 (8-9 June 1993)

For further information, contact: Academic Affairs and Postgraduate Education (MBC-36), King Faisal Specialist Hospital and Research Centre, P.O. Box 3354, Riyadh 11211, Saudi Arabia; Tel.:(01)442-7238, or Fax:(01)442-7237.

King Saud University Fellowship in Pathology

King Saud University announces the inception of a five-year joint fellowship training program in pathology. The training will be held at King Khalid University Hospital, King Faisal Specialist Hospital and Research Centre, Riyadh Armed Forces Hospital, King Fahad National Guard Hospital, and is a full-time fellowship training program. Application is open to interested and suitably qualified residents from all over the Kingdom of Saudi Arabia. To be eligible, applicants will meet the following criteria:

1. Doctors who hold an MB, BS from King Saud University or equivalent degree.

2. Doctors who have completed their internship in a recognized hospital.

3. Undergone successful completion of a selection examination and personal interview.

4. Applicants from other institutions should submit a letter from her/his employer that she/he will be sponsored during the entire period of training.

Application forms and inquiries should be forwarded to the Director of the Residency Training Program, College of Medicine, King Saud University, P.O. Box 2925, Riyadh 11461, Saudi Arabia, or contact the Residency Board secretary at Tel.:467-1551/1556/1564, or Fax:481-1853.

Fourth Gastrointestinal Endoscopy Course and Workshop, Department of Postgraduate and Academic Affairs Riyadh Armed Forces Hospital, 1993

The Fourth Gastrointestinal Endoscopy Course and Workshop will be held from 5 to 7 April 1993G(13 to 15 Shawwal 1414H).

For further information, contact: Department of Postgraduate and Academic Affairs, Riyadh Armed Forces Hospital, P.O. Box 7897, Riyadh 11159, Saudi Arabia. Tel.:(01) 477-7714; Telex: 401645 RKHPA SJ, or Fax:(01)478-1017.

Middle East Fertility Society Inaugural Meeting Thessaloniki, Greece, 1993

The Middle East Fertility Society (MEFS) will host its inaugural meeting on 26 June 1993G(6 Muharram 1414H) proceeding the Ninth Annual Meeting of the European Society for Human Reproduction and Embryology (ESHRE) meeting to be held in Thessaloniki, Greece from 27 to 30 June 1993G(7 to 10 Muharram 1414H). No registration fee is required.

For further information, contact: Secretary, Middle East Fertility Society, c/o Dr. Munir Raouf, International Hospital, P.O. Box 1084, Manama, Bahrain, or Fax:+973590495.

Diploma Program in Dermatology, Postgraduate Center for Medical Education, King Saud University, 1993

The Postgraduate Center for Medical Education, College of Medicine, King Saud University, announces the schedule for those interested for acceptance in the Dermatology Diploma Program for 1993G/1414H.

The selection examinations and interviews will be held on 17 July 1993G(27 Muharram 1414H). Deadline for submission of applications is 23 June 1993G(3 Muharram 1414).

Application forms, list of requirements, or further information can be obtained by contacting: Residency Training Program, c/o secretary, Postgraduate Center, College of Medicine, King Saud University, P.O. Box 2925, Riyadh 11461, Saudi Arabia. Tel.:467-1551/1554/1556/1564, or Fax:467-2575.

Fourth Advanced Medical Symposium, Department of Medicine, Department of Postgraduate and Academic Affairs, Riyadh Armed Forces Hospital, 1993

The Fourth Advanced Medical Symposium will be held from 17 to 19 October 1993G(2 to 4 Jumada Al-Awal 1414H).

For further information, contact: Department of Postgraduate and Academic Affairs, Riyadh Armed Forces Hospital, P.O. Box 7897, Riyadh 11159, Saudi Arabia. Tel.:(01)477-7714, extensions 4937/4936/4935/4934,or Fax:(01)478-1017.

Symposium on "The Medical Genetics in the Setting of Middle Eastern Populations", Postgraduate Center, College of Medicine, King Saud University, 1993

The College of Medicine, King Saud University, will host a symposium on "The Medical Genetics in the Setting of Middle Eastern Populations" from 26 to 28 October 1993G(11 to 13 Jumada Al-Awal 1414H) at the Postgraduate Center, College of Medicine, King Saud University, Riyadh, Saudi Arabia. Invited guest faculty include representatives from the national and international sector as well as from the Middle East.

Participants attending from abroad must obtain visa application forms provided by the Postgraduate Center in addition to submitting a curriculum vitae by 1 July 1993G(11 Muharram 1414H).

For further information, contact: Postgraduate Center; Tel.: 467-1551/1556/1564; Fax: 4811853, or Medical Biochemistry Department, Tel.:467-0830/467-1320, or Fax: 4672575.

Deadline for receipt of abstracts is 31 August 1993G(14 Rabi Al-Awal 1414H).

Lung Pathology Course, London, United Kingdom, 1993

A course in Lung Pathology will be held at the National Heart and Lung Institute, Brompton Hospital, London, United Kingdom from 26 to 29 October 1993G (11 to 14 Jumada Al-Awal 1414H).

For further information, contact: Professor B. Corrin, Pathology, Brompton Hospital, London, SW3 6NP, United Kingdom or Fax:071-351-8435 (44-71-351-8431 if outside the United Kingdom).

First International Course on Neuro-Interventional Procedures, Department of Postgraduate and Academic Affairs, Riyadh Armed Forces Hospital, 1993

The First International Course on Neuro-Interventional Procedures will be held at Riyadh Armed Forces Hospital from 7 to 9 November 1993G (23 to 25 Jumada Al-Awal 1414H).

For further information, contact: Deputy Director, Department of Postgraduate and Academic Affairs, Riyadh Armed Forces Hospital, P.O. Box 7897, Riyadh 11159, Saudi Arabia. Tel.: 477-7714, extensions 4937/4936, or Fax:478-4057/478-1017.

Saudi Ophthalmology Society (SOS)
Ophthalmology, '93

The Seventh Annual Scientific Meeting of the Saudi Ophthalmology Society (SOS) will be held from 30 November to 2 December 1993G (17 to 19 Jumada Al-Thani 1414H). This meeting will feature four courses on: (1) refractive surgery update; (2) cataract controversies; (3) glaucoma filtration surgery; and (4) diabetic retinopathy. Invited quest faculty include representatives from Europe, United States of America, and Middle East.

For further information, contact: Ophthalmology '93, Saudi Ophthalmology Society (SOS), P.O. Box 55307, Riyadh 11534, Saudi Arabia, or Fax:477-5791.

Deadline for receipt of abstracts is 1 June 1993G (11 Dhu Al-Hijjah 1413H).

Fifth Scientific Session, Saudi Heart Association, 1994

Abstracts of papers for presentation are being accepted for the Fifth Scientific Session of the Saudi Heart Association to be held in Al-Khobar (Eastern Province) Saudi Arabia, from 25 to 27 January 1994G(14 to 16 Sha'ban 1414H). Original work related to all aspects for cardiovascular diseases will be considered with particular emphasis on: (1) coronary artery disease; (2) valvular heart diseases; (3) pericardial disease; (4) interventional cardiology; (5) noninvasive cardiology; (6) infective endocarditis; (7) cardiac surgery; (8) pediatric cardiology; (9) cardiac anesthesia; and (10) congestive heart failure.

Abstracts submitted for consideration must be received by the Saudi Heart Association Organizing Committee no later than 1 September 1993G(17 Rabi Al-Thani 1414H).

For further information regarding submission of abstracts, contact: Saudi Heart Association, College of Medicine, King Saud University, P.O. Box 2925, Riyadh 11461, Saudi Arabia. Tel.: (966)(01)467-1556/1554, or Fax:(01)481-1853/467-1379.

Eighth Asian Congress of Pediatrics
New Delhi, India, 1994

The Eighth Asian Congress of Pediatrics will be held in New Delhi, India from 6 to 11 February 1994G(26 Sha'ban to 1 Ramadan 1414H).

For further information, contact: Professor RK Puri, Secretary General, Eighth Asian Congress of Pediatrics, Department of Pediatrics, Maulana Azad Medical College, New Delhi-110 002, India. Tel.:(0091)(11)331-6031/6660, or Fax: (0091)(11)228-3364.

XV Congress of the International Society of Hematology, Cancun, Mexico, 1994

The XXV Congress of the International Society of Hematology will be held in Cancun, Mexico from 17 to 22 April 1994G(6 to 11 Dhu Al-Qada 1414H)

For further information, contact: XXV Congress of the International Society of Hematology, Blvd. Dias Ordaz 808, 72530 Puebla, Mexico. Tel.:(052-22)438-100 y 373-607, or Telefax:(052-22).

First International Congress on Maxillofacial Prosthetics
Palm Springs, California, USA, 1994

The First International Congress on Maxillofacial Prosthetics will be held from 27 to 30 April 1994G(17 to 20 Dhu Al-Qada 1414H) in Palm Springs, California, USA.

Major topics include: (a) Restoration of mandibular, maxillary and facial defects; (b) Dental management of the irradiated patient; (c) Use of osseointegrated implants and free flaps in restoration of oral-facial defects; (d) Treatment of osteoradionecrosis-current concepts; (e) Materials in maxillofacial prosthetics; and (f) Osseointegrated implants in irradiated patients.

The Congress is sponsored by: 1. UCLA Maxillofacial Prosthetic Hospital Dentistry Group - Los Angeles, CA, USA; 2. Memorial Sloan-Kettering Cancer Center Dental Service - New York, NY, USA; and 3. Cleveland Clinic Dental Service - Cleveland, Ohio, USA.

For further information, contact: R.E.S. Seminars, P.O. Box 99119, San Diego, CA, USA 92109, or Fax:001-310-206-4201.

Correction

In the *Letters to the Editor* by Awada et al. "Outpatient neurological practice in Saudi Arabia and its implications for education in neurology" (1992;12(5)503-5), authors have been reversed and should read as: Saad Al-Rajeh, MD; Adnan Awada, MD; Olajide Bademosi, FRCP, MSc; Hassan Ismail, MRCP, MD. Please note this in your copies of the September 1992 issue of the *Annals*.

INFORMATION FOR AUTHORS

THE EDITORS of the *Annals of Saudi Medicine* welcome contributions from our readers. The *Annals* will consider for publication manuscripts of interest to readers in Saudi Arabia, the Middle East, and around the world. All submissions are subject to review by the Editorial Board and by referees in appropriate specialties.

Submission of Manuscripts. Manuscripts are received with the understanding that they are not under simultaneous consideration by another publication. An abstract published prior to a full report is not regarded as a duplicate publication. The author's transmittal letter must accompany the manuscript and contain these statements: "The manuscript has been seen and approved by all authors involved and is neither being published nor being considered for publication elsewhere. The authors transfer copyright to the *Annals of Saudi Medicine*." Accepted manuscripts may not be published elsewhere without *Annals'* permission.

Manuscript Preparation. The format of the *Annals of Saudi Medicine* complies with "Uniform Requirements for Manuscripts Submitted to Biomedical Journals", published by the International Committee of Medical Journal Editors in Vancouver, British Columbia, in 1979 (the widely accepted "Vancouver style"), as described in the *Annals of Internal Medicine* (1982;96 [pt 1]:766-71). With the exception of blood pressure, all units of measurement and laboratory values must be expressed in SI units; conventional units may be included parenthetically. Authors are referred to *Annals of Internal Medicine* (1987;106[1]:114-29 for guidance in the use of SI units. Manuscripts, including tables, references, and figure legends, must be typewritten, double-spaced, on 8 1/2 x 11 inch (21.5 x 28 cm) or size A4 paper, with margins of at least 1 inch (2.5 cm). Pages should be numbered consecutively, beginning with the title page and continuing through the last page of typewritten material. One original and two photocopies of the entire manuscript should be submitted, along with three sets of photographs.

Title Page. The title page must contain (1) title of the article, (2) correct names of each author plus highest academic degree for each, (3) each author's official academic and/or clinical title and affiliation, (4) name and address of the institution(s), (5) name and address of author to whom correspondence should be sent, if it differs from the first author, and (6) any disclaimers. For case reports, it is recommended that the number of authors be limited to four. Acknowledgment of support should be included in the Acknowledgment section at the end of the article.

Abstracts. All original articles must contain an abstract of not more than 200 words. The abstract should include statements of problem, method of study, results, and conclusions.

Manuscript Format. Most original articles have the following format: Introduction (the question the paper intends to answer); Material and Methods (the study design and methods, definitions such as for diagnostic criteria, the population or patient samples, and laboratory and statistical methods); Results (the pertinent findings in a logical sequence with tables and figures as necessary); and Discussion (conclusions based on the findings, evidence from the literature that supports the conclusions, conflicting evidence, applicability of the conclusions, and implications for future research or clinical applications). Authors might consult recent issues of the *Annals* for examples of appropriate format.

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المدونات الطبية السعودية مجلة تنشر بموجب الأمر الملكي السامي رقم ٥/م/٢٤٢٢٣ بتاريخ ١٤ شوال عام ١٤٠٠هـ. وتصدر مرة كل شهرين، وهي مشروع مشترك بين كل من كلية الطب ومستشفى الملك خالد الجامعي - جامعة الملك سعود، صندوق بريد ٢٩٢٥ - الرياض ١١٤٦١، المملكة العربية السعودية، ومستشفى الملك فيصل التخصصي ومركز الأبحاث، صندوق بريد ٣٣٥٤ - الرياض ١١٢١١، المملكة العربية السعودية. يتم صف وطبع المجلة بمطابع جامعة الملك سعود. يتم توزيع المدوَّنات بواسطة قسم البريد التابع لإدارة الخدمات الإدارية بمستشفى الملك فيصل التخصصي ومركز الأبحاث. كما يتولى قسم الترجمة في هذه الإدارة إعداد الملخصات العربية بالاشتراك مع الدكتور محمد زهير القاوي. كل المراسلات والاستفسارات وطرق الحصول على المستلات ترسل إلى مكتب المطبوعات على العنوان التالي:

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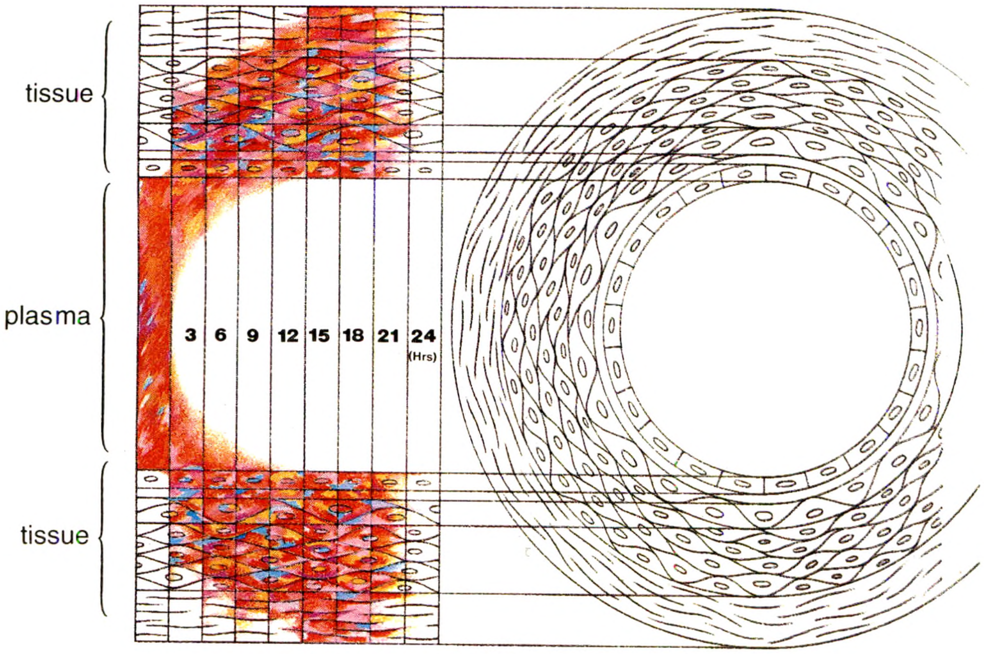

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